PBBM to Assess Food Effect in Pediatric Patients

Presented at PQRI Workshop: Model-Informed Drug Development (MIDD) Approaches in Pediatric Formulation Development

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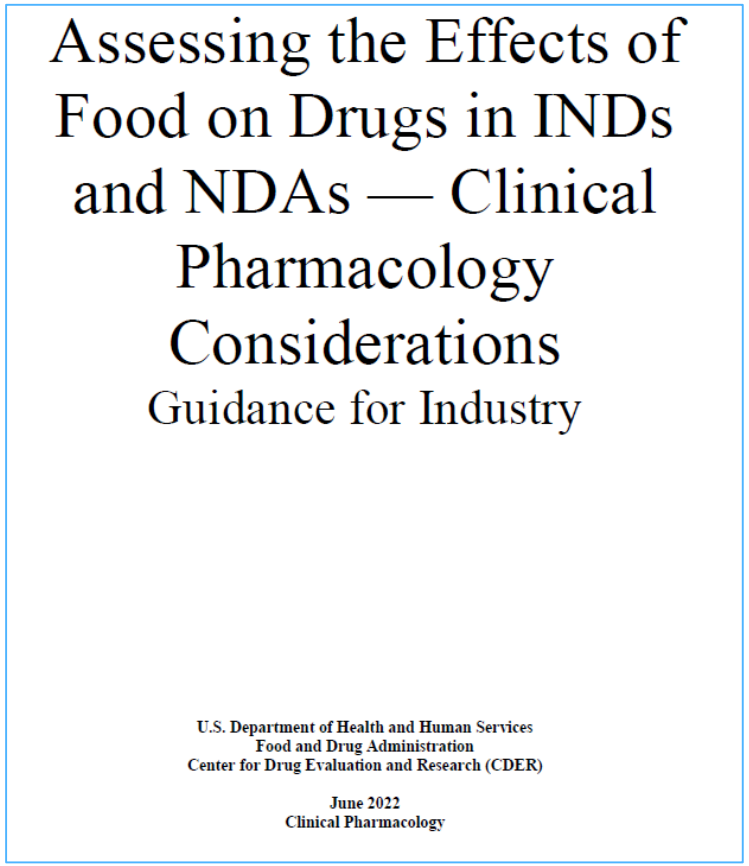
Food effects are usually assessed in adults

FDA Food Effect Guidance 2022

- Adult FE study is usually a single-dose, two-treatment (fed and fasted), two-period, crossover design in healthy volunteers
- A high-fat meal (and other meal types as needed)
- Ethical reasons severely limit food effect study conduct in pediatric patients
- «When a new age-appropriate pediatric formulation is developed, the sponsor should conduct a new FE study with the pediatric formulation in adults. These results can then be applied to the pediatric population.»


Assessing the Effects of Food on Drugs in INDs and NDAs — Clinical Pharmacology Considerations

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2022
Clinical Pharmacology

But can food effect in adults be transferred directly to children?

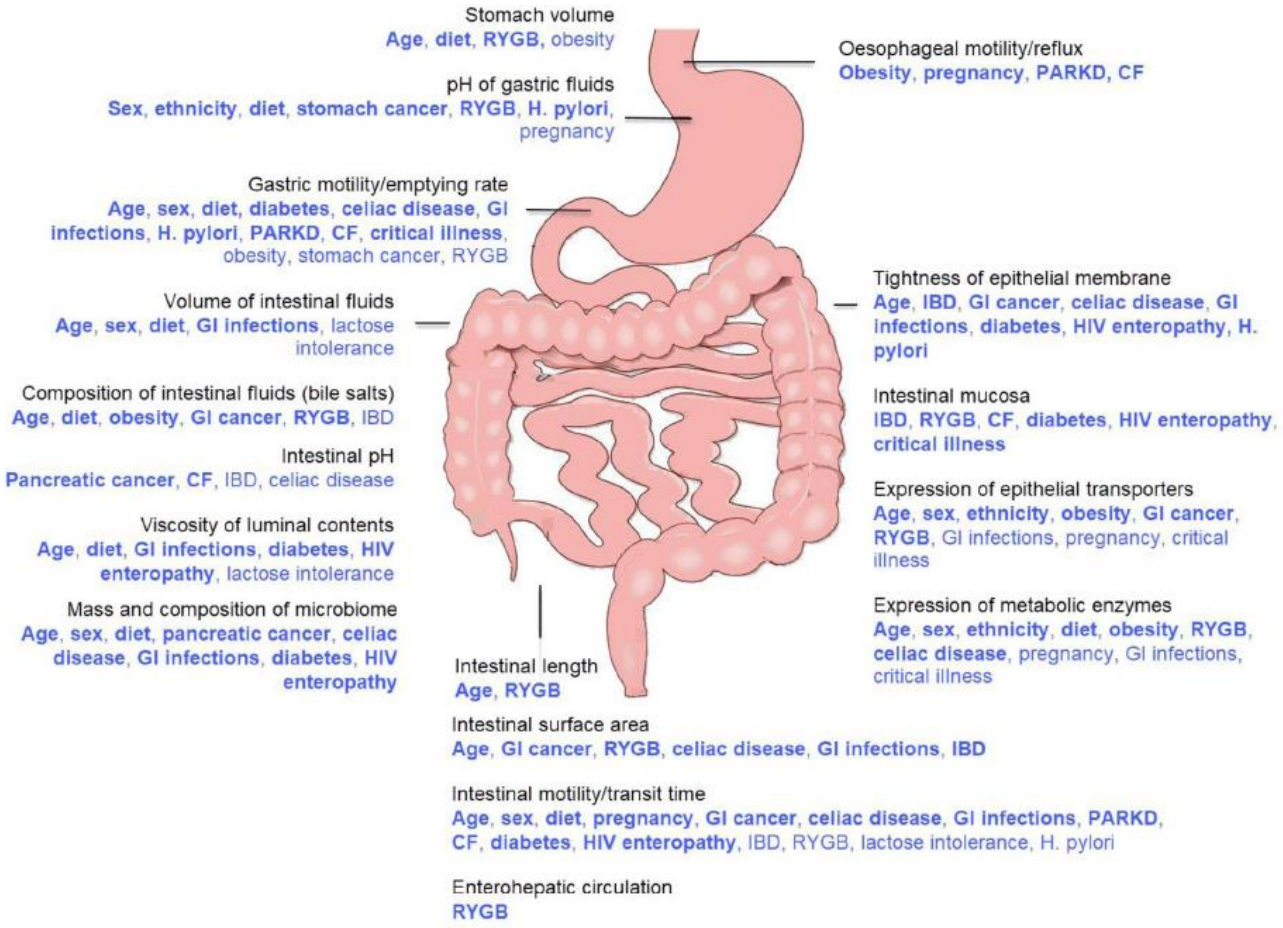
Influence of Food on Paediatric Gastrointestinal Drug Absorption Following Oral Administration: A Review

Hannah K. Batchelor. Children 2015, 2, 244-271;

- Differences in pediatric physiology may affect food-drug interactions
- Additional research is required to understand the physiological and anatomical factors that can influence the absorption of a drug in pediatric populations
- Differences in dietary composition and feeding patterns may affect food-drug interactions
- There is insufficient evidence to justify extrapolation of existing methods used to predict food effects in adults directly to pediatric populations

Age dependent changes in GI physiology

Stillhart et al, European Journal of Pharmaceutical Sciences, 147, 2020, 1-28



Changes known to cause food effects in adults are age dependent e.g.

- stomach volume
- pH (stomach and upper SI)
- gastric emptying time
- bile salt concentrations
- liver blood flow

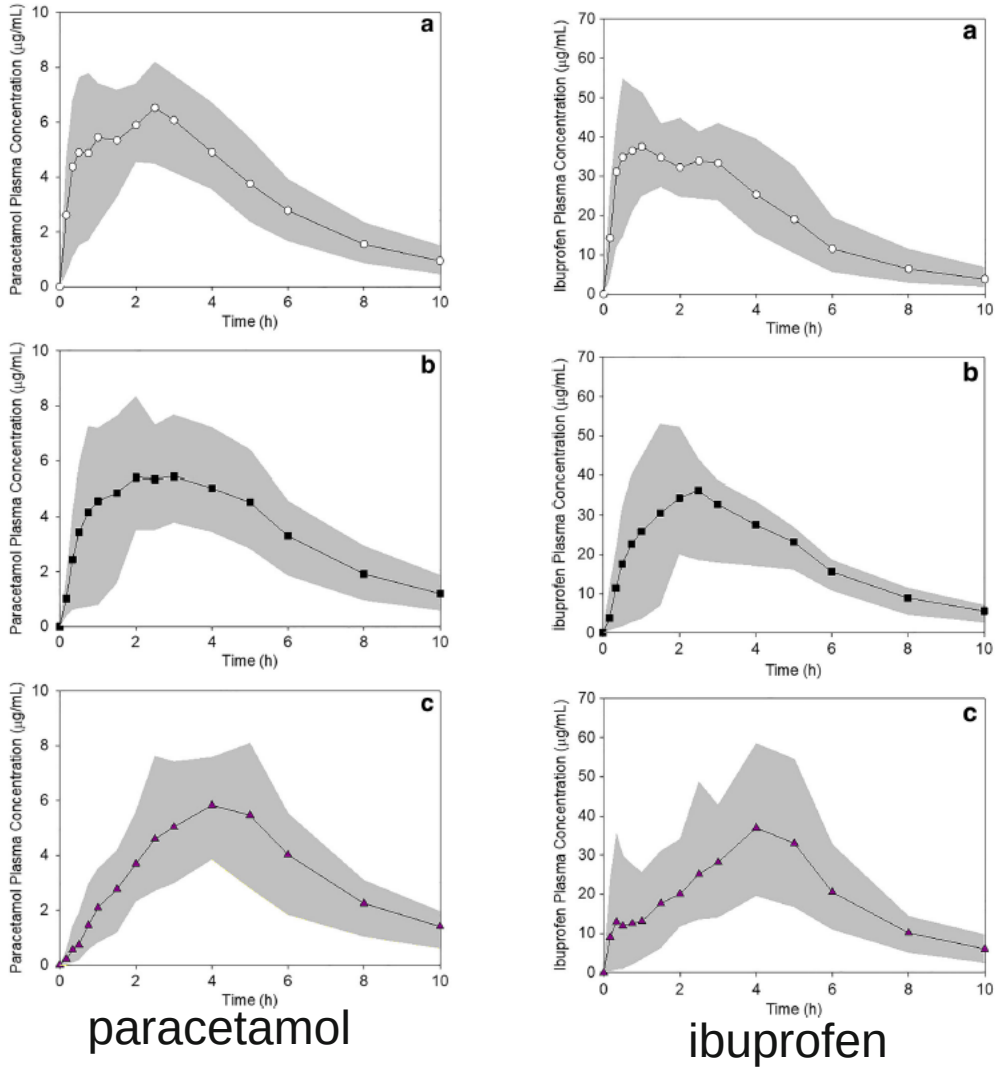
Differences in pediatric meals and feeding patterns

Statelova M, Goumas K, Fotaki N, Holm R, Symillides M, Reppas C, et al. On the design of food effect studies in adults for extrapolating oral drug absorption data to infants : an exploratory study highlighting the importance of infant food. AAPS J. 2020;22(6):1–11.

fasted

fed

Infant fed



paracetamol

ibuprofen

- Paracetamol and ibuprofen pediatric suspensions dosed in adults
- No significant differences in AUC but absorption rate with the infant meal (520 kcal formula) was slower than fasted state absorption rate and also slower than adult fed state (990 kcal standard meal)
- Differences in food type can cause differences in fed PK
- The question remains : Do adults fed with pediatric meals adequately represent the situation in infants?
- Both physiological and food type may be important.

Differences in pediatric meals and feeding patterns

Food-Drug Effects and Pediatric Drug Development Studies Submitted to the US Food and Drug Administration, 2012-2022
Tunehag et al. The Journal of Clinical Pharmacology 2024

- Identified oral drug products with FE observed in adults and approved for use in pediatric patients
- Of 102 products approved in <6 year olds, 43 recommended the consideration of food in the drug label
- 14 drug products are recommended to be taken **without food** in pediatric patients aged <2 years
  - But children feed frequently and tend to remain semi-fed
- For drug products recommended **with food** labeling often does not specify type of food and infant diets do not resemble adult diets
- For none of these drugs has the food effect been confirmed in children

Clinical evidence that adult food effect transfers to children?

Statelova M, Goumas K, Fotaki N, Holm R, Symillides M, Reppas C, et al. On the design of food effect studies in adults for extrapolating oral drug absorption data to infants : an exploratory study highlighting the importance of infant food. AAPS J. 2020;22(6):1–11.

- Very limited number of FE studies have been performed in children (~25)

- Clinical studies with 7 antibiotic susensions indicate differences

	FE infants	FE Adults
Fed Ampicillin	none	negative
Penicillin G	negative	none
Penicillin V	negative	none
Amoxicillin	none	negative
Cephalexin	negative	none
Erythromycin Estolate	none	positive
Erythromycin ethyl-succinate	positive	positive

Is there a better way to project food effect in children?

Physiologically based biopharmaceutics modeling (PBBM)

- PBBM is that part of PBPK which focuses on the integration of drug substance properties and formulation characteristics with system physiological parameters to predict the absorption of a drug product
- PBBM makes up >20% of publications in PBPK[1]
- Key applications in drug development include
  - formulation selection and development
  - food effect evaluation
  - pH-dependent drug-drug-interaction risk assessment
- PBBM also is increasingly used in NDA submissions to support drug product quality[2]
  - biopredictive dissolution method development
  - biopharmaceutics risk assessment
  - clinically relevant specification settings
  - VBE

1 El Khateeb 2020

2 Wu Pharmaceutical Research (2023)

Pediatric PBPK (p-PBPK) and PBBM (p-PBBM)

- A growth of p-PBPK models in both drug development and clinical settings has been noted
  - 33-fold increase between 2005 and 2020[1]
- p-PBPK can be valuable for pediatric drug development because of
  - small number of patients
  - ethical complexities
  - rapid development of physiological characteristics
- However many models use simple absorption descriptions and PBBM for pediatrics certainly remains underused

1 Johnson 2022

PBBM for food effects in adults

- PBPK has been applied for food effect predictions over many years due to its ability to integrate drug specific data with physiological changes

Predicting Pharmacokinetic Food Effects Using Biorelevant Solubility Media and Physiologically Based Modelling

Hannah M. Jones,[1] Neil Parrott,[1] Gerd Ohlenbusch[2] and Thierry Lavé[1]

1 Drug Metabolism and Pharmacokinetics, F. Hoffmann-La Roche Ltd, Basel, Switzerland
2 Pharmaceutical and Analytical R&D, F. Hoffmann-La Roche Ltd, Basel, Switzerland

Changes in Fasted vs Fed state:
- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Higher liver blood flow

- Multiple publications have shown good simulation of positive food effects seen with lipophilic and permeable drugs
- However regulatory impact has been limited due to lack of confidence

IQ evaluation of food effect prediction

Riedmaier et al. Use of physiologically based pharmacokinetic (PBPK) modeling for predicting drug-food interactions: an industry perspective. AAPS J. 2020;22:123.

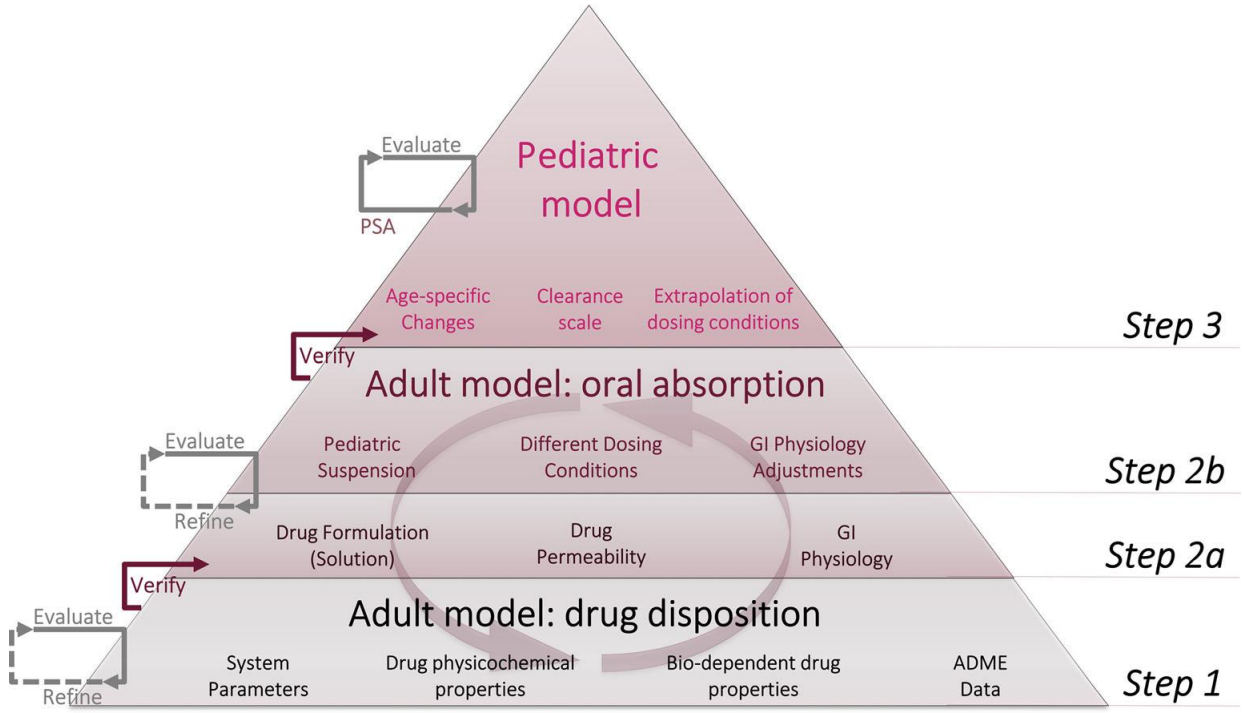
- Performed an analysis of the confidence in PBPK food effect prediction
  - 30 compounds with diverse BCS class and food effect (+ve, -ve, no change)
  - Consistent model building approach
- Food effect predicted with high (1.25-fold) or moderate (2-fold) confidence for 80% of compounds
- Confidence is associated with known and predictable mechanisms (GI solubility and physiology changes)
- Gaps are apparent when mechanisms are complex and in vitro tools lacking

PBBM strategy for predictions in children

PBBM based translation of food effect to children

Statelova M et al. Successful Extrapolation of Paracetamol Exposure from Adults to Infants After Oral Administration of a Pediatric Aqueous Suspension Is Highly Dependent on the Study Dosing Conditions. The AAPS Journal (2020) 22: 126

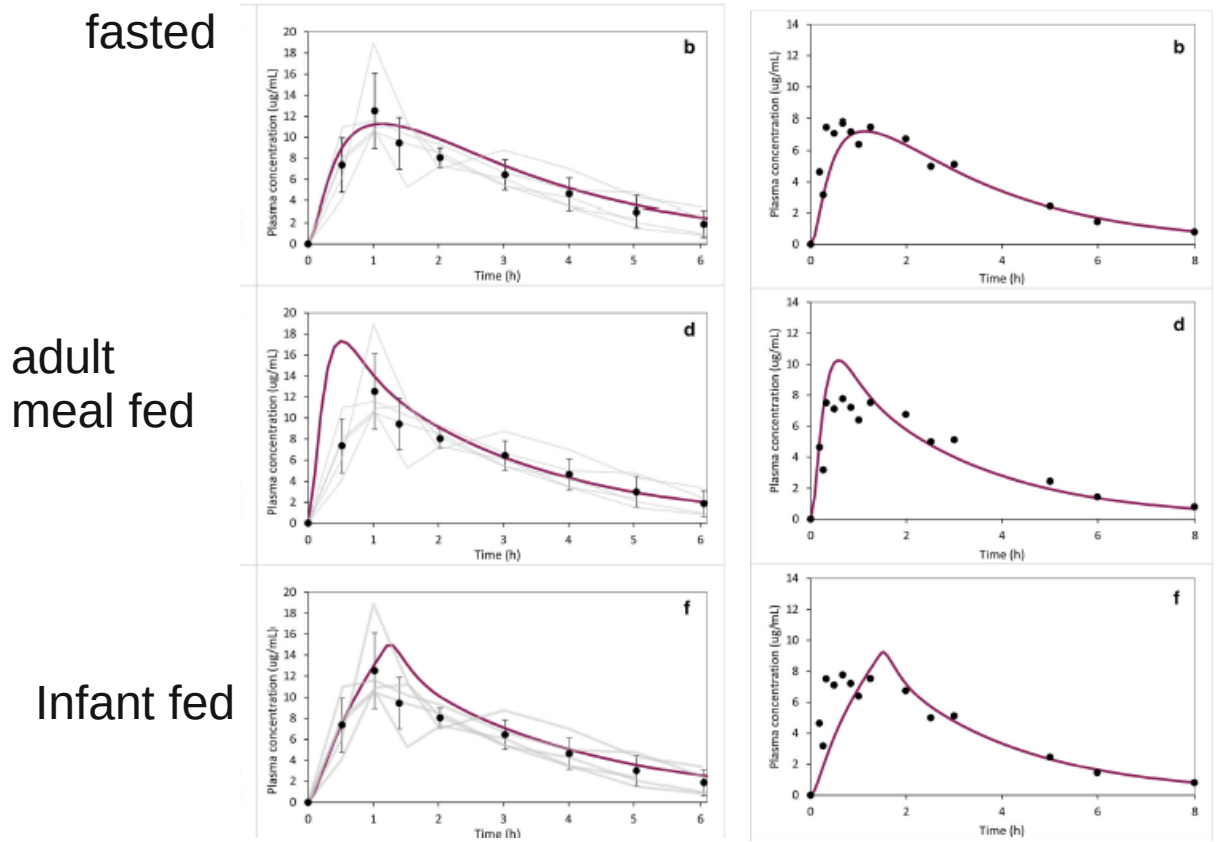
- Disposition models verified in adults
- PBBM optimized with adult data for pediatric formulation
- Disposition scaled to infants using PBPK
- Adult PBBM scaled to infants using optimized model with age-specific changes and refinements for dosing conditions



PBBM based food effect translation to infants : paracetamol

Statelova M et al. Successful Extrapolation of Paracetamol Exposure from Adults to Infants After Oral Administration of a Pediatric Aqueous Suspension Is Highly Dependent on the Study Dosing Conditions. The AAPS Journal (2020) 22: 126

- Adult data was necessary to inform fasted and fed state gastric emptying behaviors of the pediatric suspension as model defaults were not accurate
- fasted conditions and infant-formula fed conditions resulted in successful predictions but not adult meal fed conditions
- GTT and gastric emptying kinetics needed to be scaled from the adult data based on meal calories

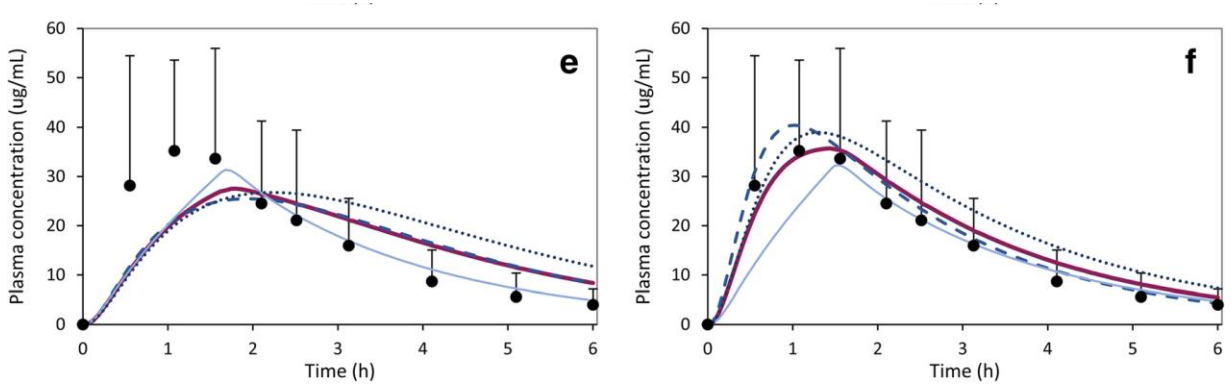


NB: fed status of the infants was not known but infant fed is most likely

PBBM based food effect translation to children : ibuprofen

Statelova M et al. Factors Affecting Successful Extrapolation of Ibuprofen Exposure from Adults to Pediatric Populations After Oral Administration of a Pediatric Aqueous Suspension. The AAPS Journal (2020) 22: 146

- usefulness of adult PK data collected for pediatric ibuprofen suspension was confirmed
- Using optimized GTT adjusted for pediatric food gave superior predictions to default fed state GTT



default GTT

adjusted GTT values

Pediatric PBBM examples

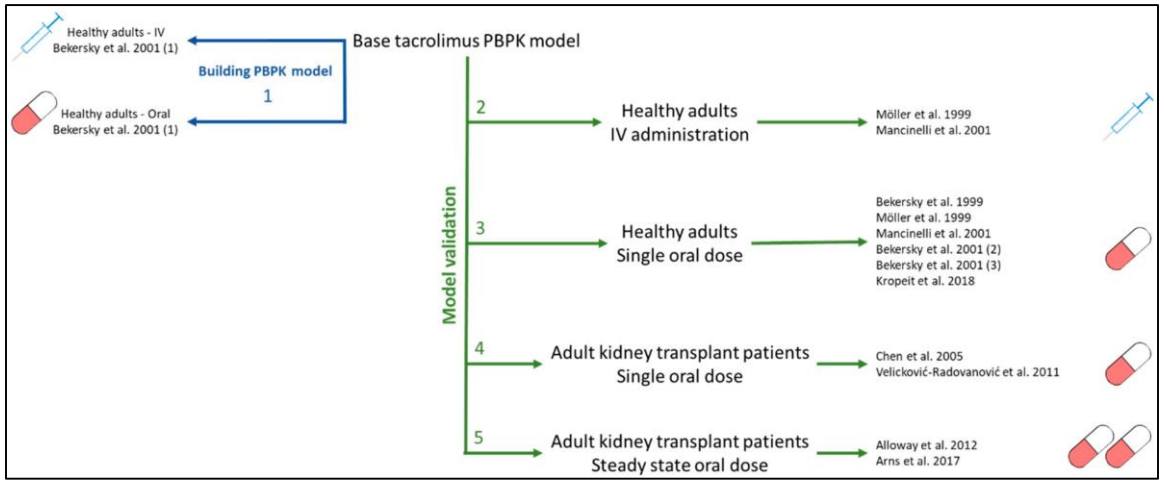
Tacrolimus p-PBBM example

Matthias Van der Veken et al. Investigating Tacrolimus Disposition in Paediatric Patients with a Physiologically Based Pharmacokinetic Model Incorporating CYP3A4 Ontogeny, Mechanistic Absorption and Red Blood Cell Binding. Pharmaceutics 2023, 15, 2231.

- An immunosuppressant used for organ transplant patients
- BCS 2 - low crystalline solubility and high permeability - formulated as ASD
- High PK variability
- Therapeutic drug monitoring means that we find rich PK data covering a wide age range in children
- A good candidate to explore p-PBBM

Tacrolimus p-PBBM example : workflow

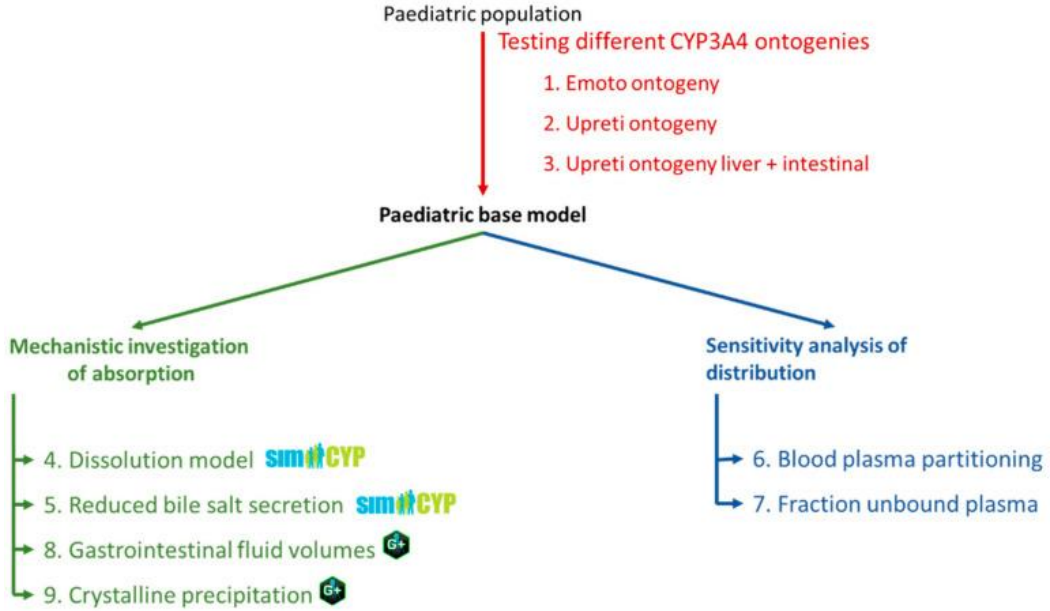
Adult model verification



Steps taken:

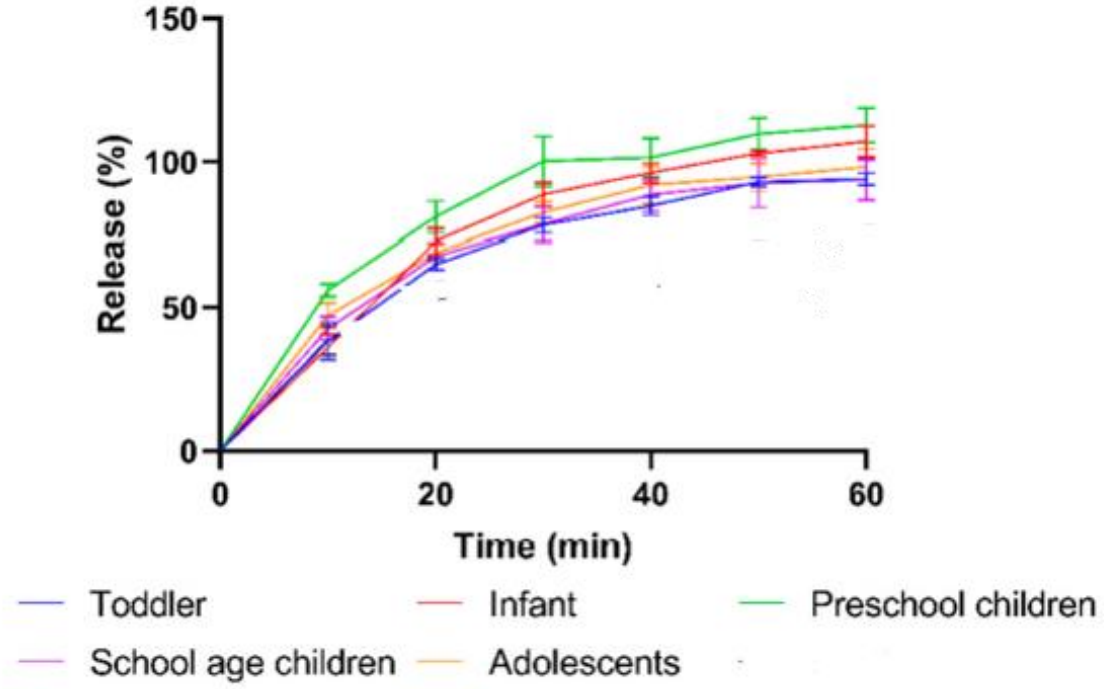
- Build and verify adult PBPK / PBBM

- Apply to pediatrics
  - Custom dissolution testing in pediatrics
  - Sensitivity analyses for Fabs%
  - Explore absorption, distribution and metabolism uncertainties and compare to observed data



Tacrolimus p-PBBM example : in vitro data

- Dissolution experiments in FaSSIF with custom conditions for pediatric sub-populations based on doses and with fluid volumes as measured in children using MRI *



similar fast and extensive dissolution of the amorphous formulation

Infant (0.1–1 year)
Toddler (1–2 year)
Preschool child (2–5 year)
School-age child (6–11 year)
Adolescent (12–16 year)
Adult

* Matthias Van der Veken et al. Gastrointestinal Fluid Volumes in Pediatrics: A Retrospective MRI Study. Pharmaceutics 2022;14(9):1935.

Tacrolimus p-PBBM example : model sensitivity analysis

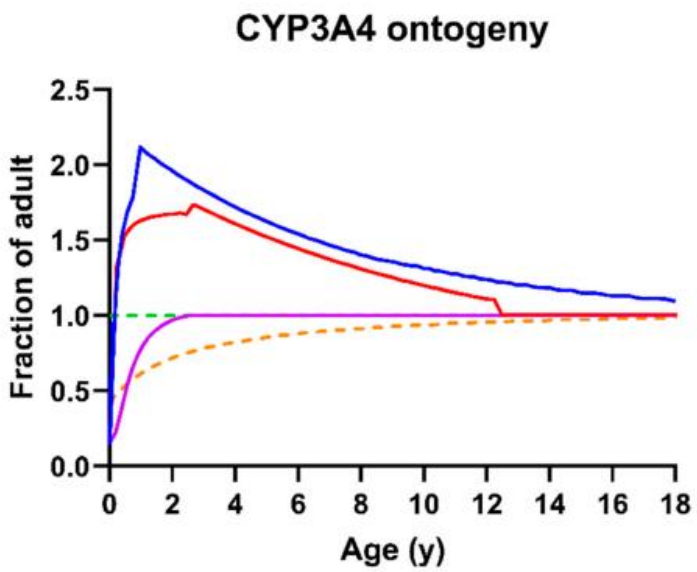
- Fraction absorbed sensitivity analyses for ASD
  - Input of measured dissolution profiles showed low impact on simulated PK
  - Impact of a decreased bile salt concentration showed low sensitivity
- Small intestinal water volume (range from min to max of measured SIFV*)
  - low sensitivity for ASD : fraction absorbed varied by <1%
  - higher sensitivity for crystalline drug : fraction absorbed varied by ~20%
- Precipitation time : low sensitivity

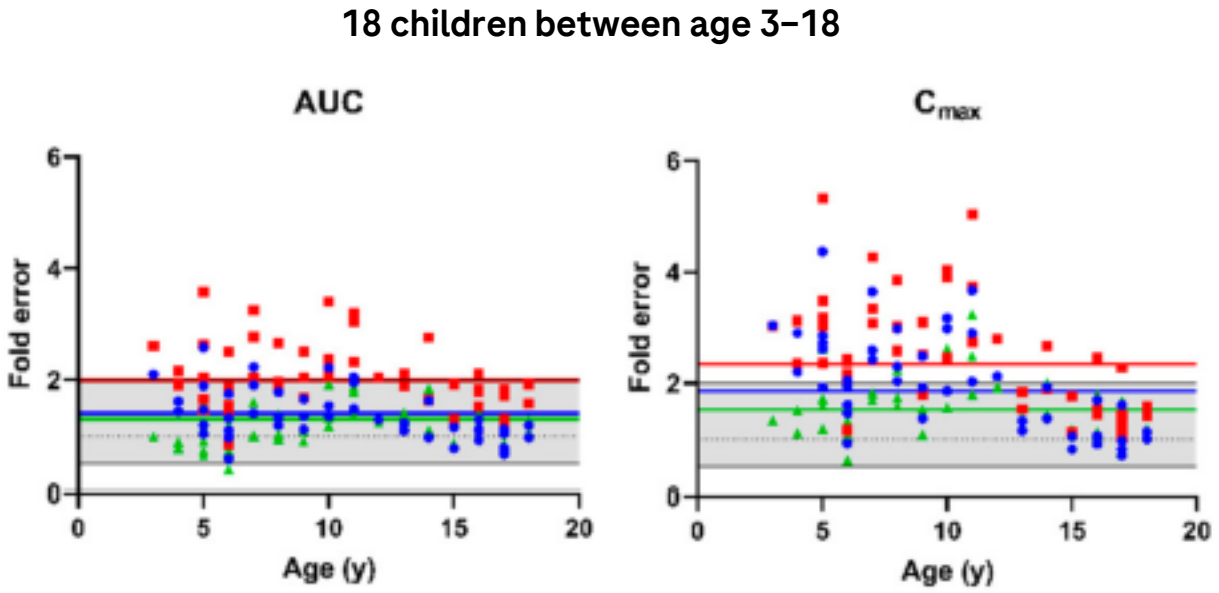
- Even though crystalline tacrolimus is BCS 2 the ASD behaves more like BCS 1

* Matthias Van der Veken et al. Gastrointestinal Fluid Volumes in Pediatrics: A Retrospective MRI Study. Pharmaceutics 2022;14(9):1935.

Tacrolimus p-PBBM example : model sensitivity analysis

- High first pass in gut and liver and uncertainty in CYP3A ontogeny leads to high sensitivity





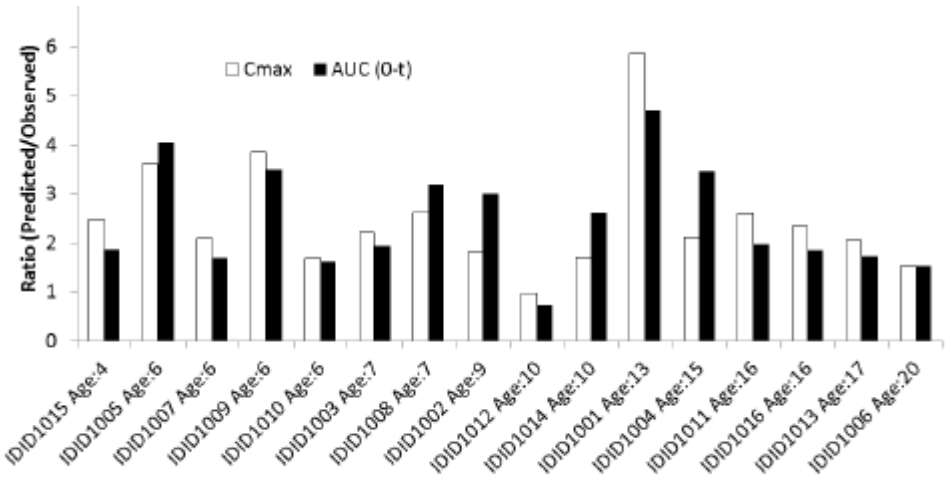
p-PBBM example

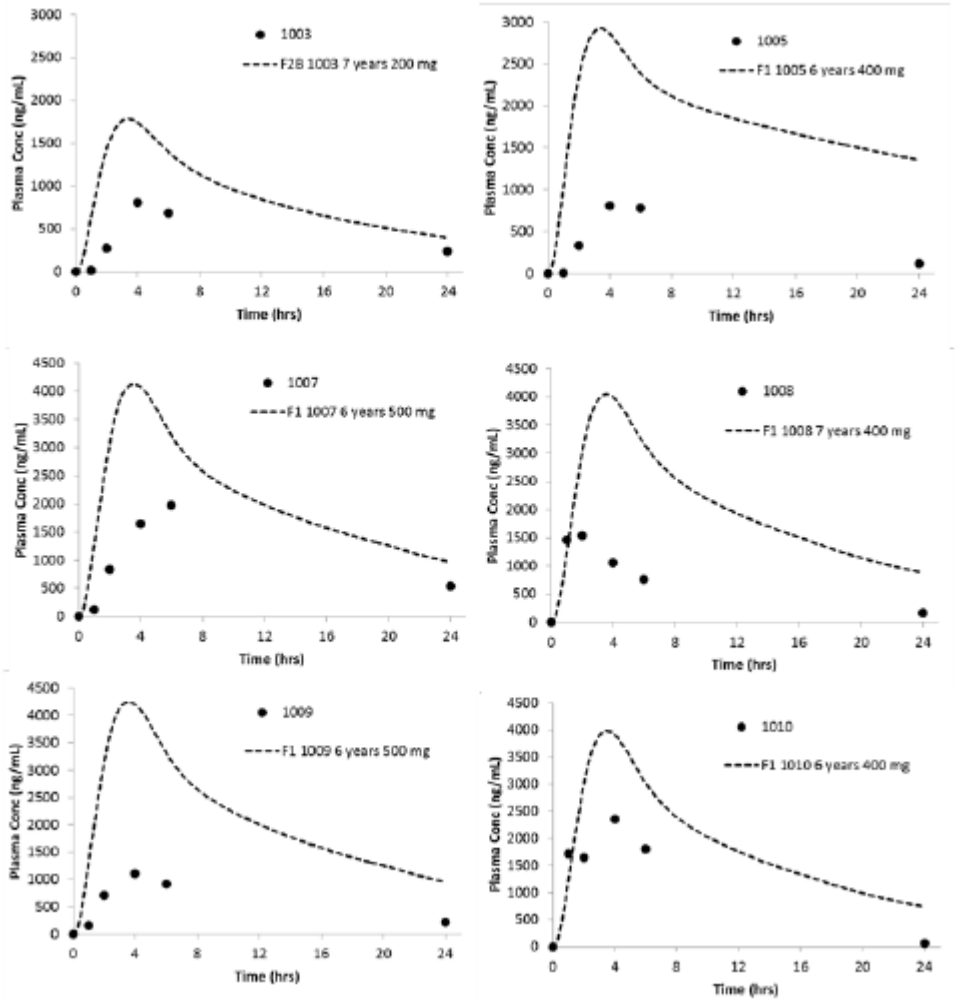
- Weak base
- Reasonable permeability
- Highly pH dependent aqueous solubility
- Strong effect of bile salts on solubility
- No precipitation in vitro
- No IV data
- CYP3A substrate (Itraconazole study used to estimate Fg)
- Food effect with earlier formulation F1 could be removed via optimized formulation F6
- Limited data in children mostly obtained with F1

p-PBBM example : impact of bile salt solubilization

BSSR based on a standard adult meal (high fat/ high calorie) in NHVs

- Children were fed but food type not well controlled
- BSSR based on FeSSIF solubility leads to over prediction of AUC and Cmax by ~2.5 fold

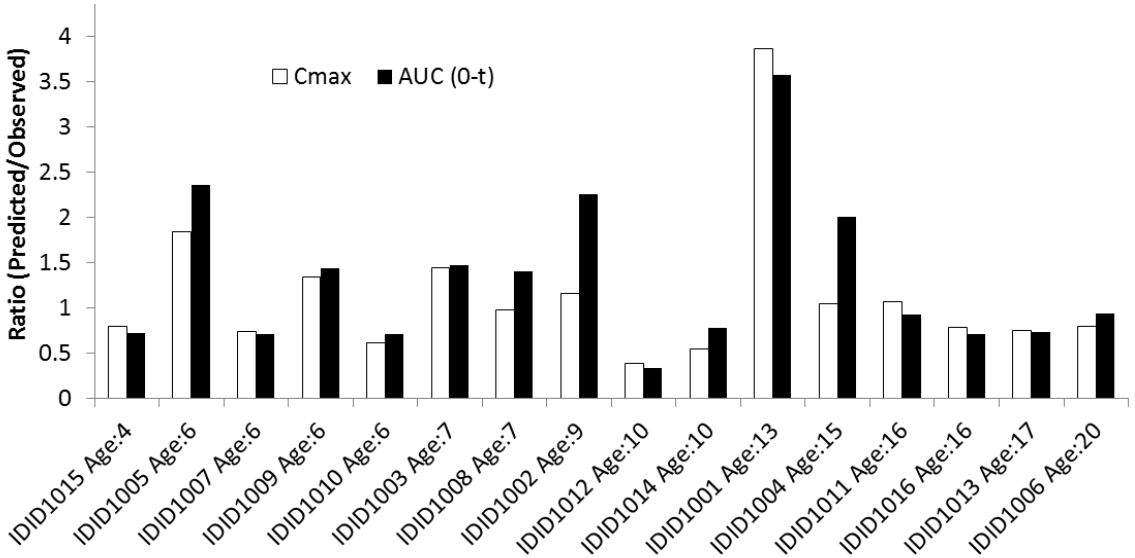


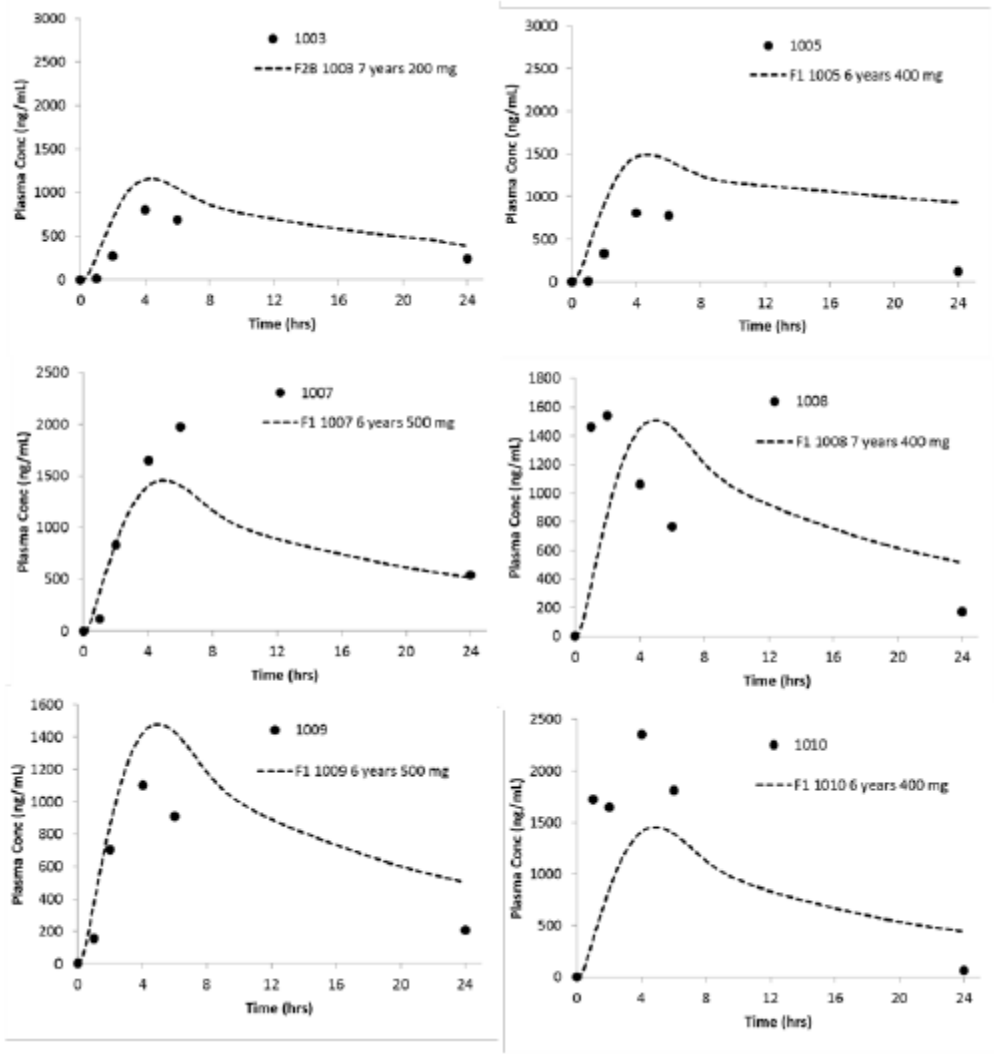


p-PBBM example : impact of bile salt solubilization

BSSR representative of a lighter meal

- Reduced BSSR can better capture the observed food effect for these children





Knowledge gaps limiting p-PBBM

Wollmer et al. Review of paediatric gastrointestinal physiology relevant to the absorption of orally administered medicines. Advanced Drug Delivery Reviews 2022

Parameter	Newborns	Infants	Toddlers	Pre-school	School	Adolescents	Adults
Gastric emptying	+	+	(+)	+	+	+	+
Fasted gastric fluid volume	–	(+)	–	(+)	+	+	+
Fasted gastric pH	+	–	–	(+)	+	+	+
Duodenal bile salts	+	(+)	–	(+)	(+)	(+)	+
SI transit time	(+)	(+)	(+)	(+)	+	+	+

+ adequate and reliable data available
(+) very limited data available
- no data available.

Adapted from *Wollmer et al.*

knowledge gaps in ontogeny of GI physiology are one cutrent limitation of p-PBBM

Conclusions

Knowledge Gaps and Challenges in PBBM for food effects in children

- Methods are needed to project food effects for children which account for age-dependent changes in physiology and differences in formulation, food-type and feeding patterns
- PBBM provides a framework integrating knowledge on age dependent physiology and food effect mechanisms
- PBBM has shown value for projection of food effects in adults, however mechanisms for food and formulation effects can be complex and models need improvement
- There are gaps in our knowledge of the ontogeny of the pediatric GI tract
- Clinical data on pediatric oral PK are limited and the PK of many clinically used pediatric drugs can be complex

- Pediatric PBBM should play a key role in advancing our methods for prediction of pediatric doses by integrating growing knowledge on physiology development with biorelevant in vitro and clinical data

Doing now what patients need next