Predictive Performance of PBPK Dose Estimates for Pediatric Trials


Dr. Ibrahim Ince
Dr. André Dallmann

Bayer AG

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Conflicts of interest / disclaimer

All authors are full time employees of Bayer AG

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PBPK modelling has been the scientific foundation for predictive exposure matching based on clinical studies for almost 2 decades

- Physiology based pharmacokinetic (PBPK) models have often supported the development and guidance of dosing strategies in children.
- These models incorporate age dependent changes of the relevant anthropometric and physiological parameters and apply ontogeny and variability of active processes involved in the elimination of pharmaceutical compounds.
- As most changes occur in the first 2 years of life, a good understanding of age-related changes in these processes is of upmost importance.
- Several studies have been performed for Bayer compounds, applying dosing schemes in children based on PBPK predictions.

PBPK modeling in adults and translation to children in Open Systems Pharmacology (PK-Sim / MoBi)

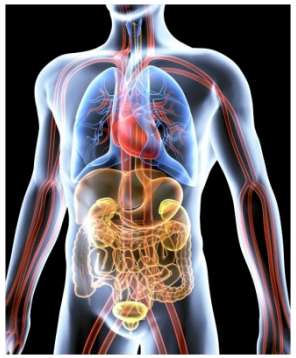
Building blocks of a PBPK model for adults

Drug properties

Physicochemical properties
- Lipophilicity
- Molecular weight
- pKa/pKb

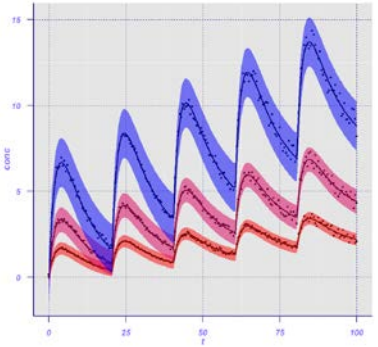
Drug-biology interaction
- Fraction unbound
- Partition coefficients
- Mass Balance
- Fractional CL contributions
- Permeability
- Active processes (K_m, V_{max})

Organism properties



Anatomy & physiology
- Organ volumes
- Surface areas
- Tissue composition
- Blood flow rates
- Expression levels

Study protocol and formulation properties



Formulation
(empirical or mechanistic dissolution function)

Administration protocol
(dose and dosing regimen)

Special events
(food intake, exercise, EHC)

Building blocks of a PBPK model for children

Drug properties

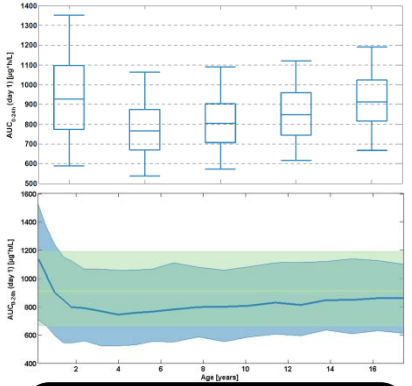
Physicochemical properties
- Lipophilicity
- Molecular weight
- pKa/pKb

Resulting age-dependent changes in drug-biology interaction

Organism properties

Age-dependent changes in anatomy & physiology

Study protocol and formulation properties



Modified formulations
(e.g. minitablets, syrup)

Adjusted administration protocol
(e.g. mg/kg dosing)

Different special events

Bridging from adults to children - Workflow

Step 1:

Development and verification
of a PBPK model for adults

Step 2:

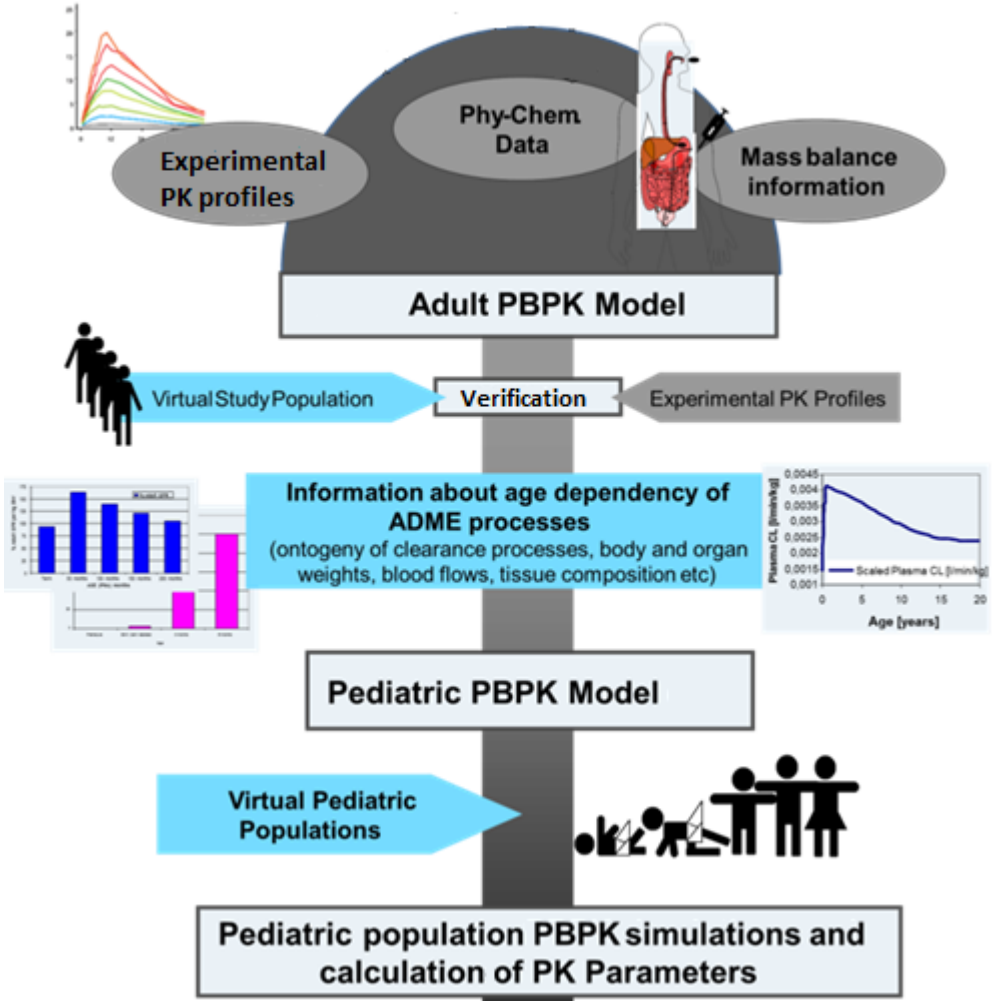
Translation of the adult PBPK model
to children using prior physiological information
about growth and maturation of relevant
processes

Step 3:

Prediction of pharmacokinetics
in children by means of simulations of virtual
pediatric trials

Step 4:

Support of clinical decision process by evaluating
adequate dosing, sampling or cohort size



Ince I. et al. J. Clin. Pharmacol. 59(S1), 2019

Pediatric dosing schemes in children supported by PBPK predictions

Overview of Bayer small molecule compounds applied in children since 2005

Market Name	Age range (years)	Involved processes in PBPK model
Amikacin	0.01 – 16	GFR
Ciprofloxacin	0.2 – 6.6	CYP1A2, TS, GFR, Bil.CL
Copanlisib	13 – 17	CYP3A4, PgP, PIK3a
Gadovist	0.2 – 18	GFR
Levonorgestrel	12 – 18	Hepatic CL
Magnevist	0.2 – 2	GFR
Moxifloxacin	0 – 18	UGT1A1, SULT2A1, Bil.CL, TS/GFR
Regorafenib	2 – 17	CYP3A4, UGT1A9, Bil.CL
Riociguat	6 – 18	CYP1A1, CYP3A4, CYP3A5, CYP2C8, CYP2J2,UGT1A2, UGT1A9, Bil.CL (Pgp, BCRP), TS/GFR
Rivaroxaban	0 – 18	CYP3A4, Plasma Hydrolysis, GFR, TS, CYP2J2
Sorafenib	1 – 19	CYP3A4, UGT1A9, Reduction, Unspecific CL

** TS : tubular secretion, Bil.CL: biliary clearance, PIK3a: phosphatidylinositol 3-kinase alpha*

Prospective evaluation of PBPK predictions with data observed during clinical studies in children are continuously performed

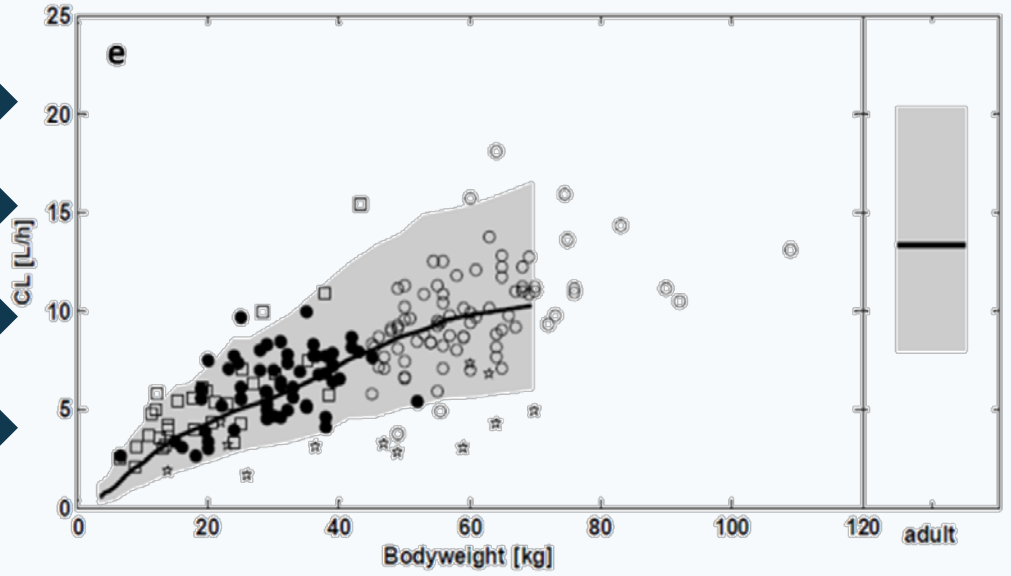
SULT2A1

UGT1A1

biliary

renal

Example: Moxifloxacin



- black line: PBPK prediction for children (median)
- gray shaded area: PBPK prediction for children (90% interval)
- symbols: individual data derived from clinical observations using population PK modelling in pediatric phase 1 and 3 trials following single or multiple oral or intravenous doses

Willmann et al., *J Clin Pharmacol.* (2019)

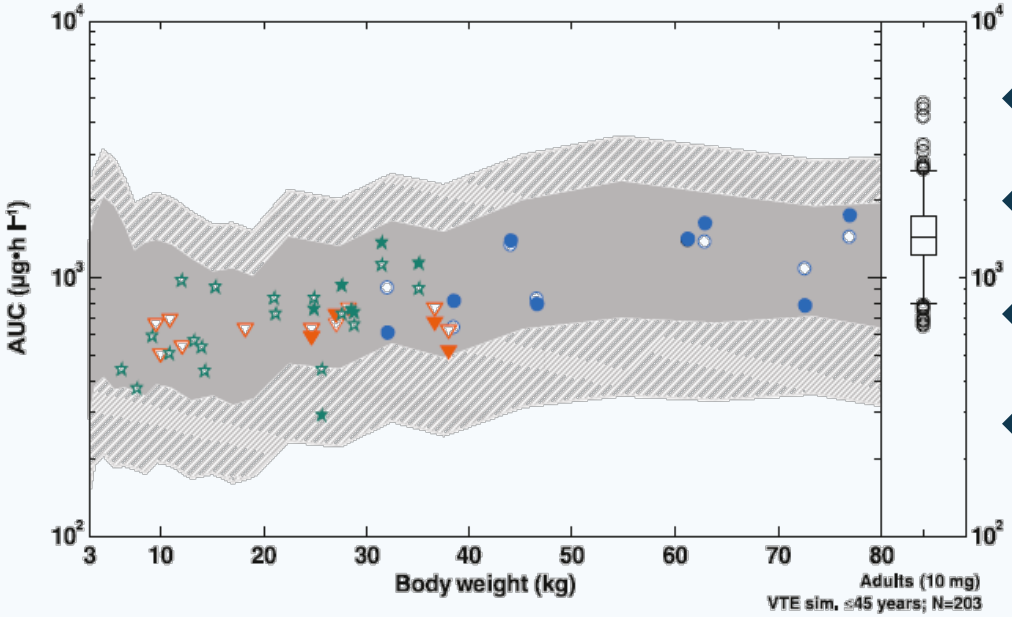
CYP3A4

CYP2J2

hydrolysis

renal

Example: Rivaroxaban



- dark gray area: PBPK prediction for children (90% interval)
- light gray area: extended PBPK prediction range (0.5 x 5th to 1.5 x 95th percentile)
- symbols: individual data derived from clinical observations following single administration of 10 mg-equivalent dose

Willmann et al., *Thrombosis Journal* (2018)

Evaluation of 10 Bayer Compounds applied in Children

// Evaluated pediatric PBPK models for 10 Bayer compounds

// Via Ratio-calculation PBPK vs reported PK (popPK and NCA of clinical data)

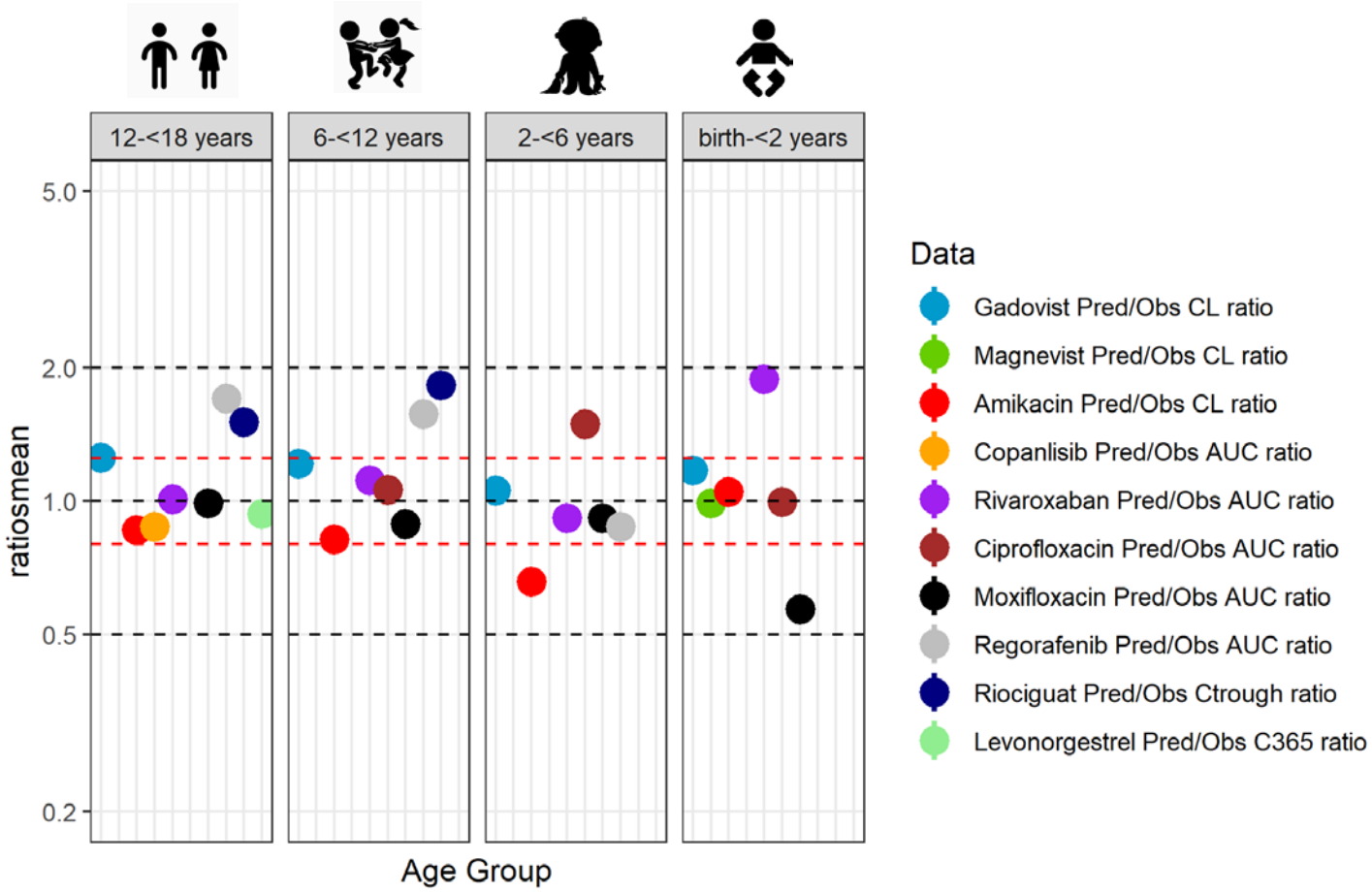
Evaluation of predictive performance	**Ratio of Predicted PBPK vs PopPK and NCA of clinical data-based PK-Parameters** **$AUC_{24,ss}$** **C_{trough}** **$C_{365days}$** **Clearance**
Predefined age groups	**0-<2** years **2-<6** years **6-<12** years **12-<18** years
PBPK simulation software	Open Systems Pharmacology **(OSP)** Suite (PK-Sim / MoBi) * (or formerly BTS Computational Systems Biology Suite)
Calculation & Illustration software	**Rstudio** Version 1.2.5033

** http://www.open-systems-pharmacology.org/*

Confirmation of predictive power of PBPK

Predicted versus observed

- **For all pediatric age groups**
  - **100% of observed data within 2-fold range of prediction**
  - **67% within BE interval**



Discussion

- Successful and adequate prediction of PBPK models for 10 compounds
  - Clear illustration of the predictive power of PBPK for guiding dosing schemes for compounds in the pediatric population.

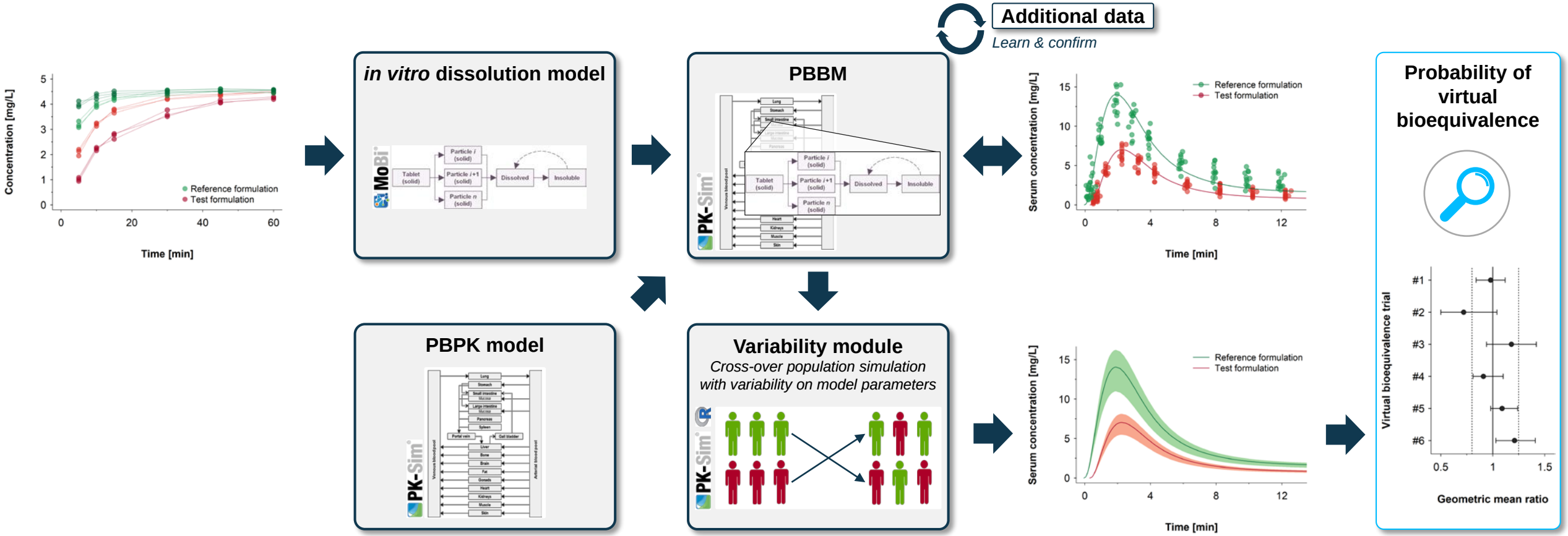
- Distribution and clearance in children are now relatively well understood, whereas dissolution and absorption often lack a more systematic and mechanistic understanding [1]

- The use of PBPK modeling for biopharmaceutics applications in adults and children is an area of ongoing research

[1] Ince I. et al. *J. Clin. Pharmacol.* 59(S1), 2019. https://doi.org/10.1002/jcph.1497

Filling the gap: PBPK modeling for biopharmaceutics applications

Workflow for virtual bioequivalence testing



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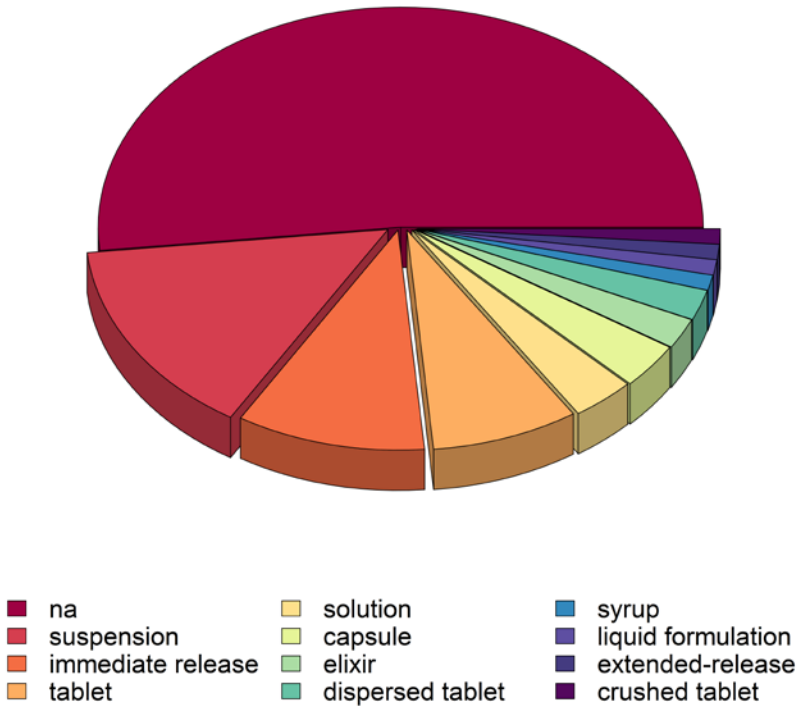
Filling the gap: PBPK modeling for biopharmaceutics applications

- FDA encourages the use of PBPK modeling for bio-pharmaceutics applications under certain conditions [1]
- Pediatric PBPK models for oral drug formulations haven been successfully used to predict drug pharmacokinetics
- Recently, first efforts were made to use pediatric PBPK models for virtual bioequivalence assessment [2,3]
- Biorelevant media are unlikely to be biopredictive for children; adaptations may be required
- Technical frameworks for virtual bioequivalence testing with OSP are being developed

Oral dosage forms in published pediatric PBPK models (*n* = 89)



[1] FDA Draft Guidance for Industry: The Use of Physiologically Based Pharmacokinetic Analyses — Biopharmaceutics Applications for Oral Drug Product Development, Manufacturing Changes, and Controls. September 2020.

[2] Vaidhyanathan S. et al. *J. Pharm. Sci.* 108(1), 2019. https://doi.org/10.1016/j.xphs.2018.11.005

[3] Miao L et al. *AAPS J.* 22(107), 2020. https://doi.org/10.1208/s12248-020-00493-6

Thank you!

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