Dose Prediction and Modelling and Simulation - Industry Perspective

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Disclosures - ML is an employee and stockholder of AstraZeneca

FDA-University of Maryland CERSI Public Workshop:
Development of Antihypertensive Therapies for Use in Pediatric Patients

16 July 2026

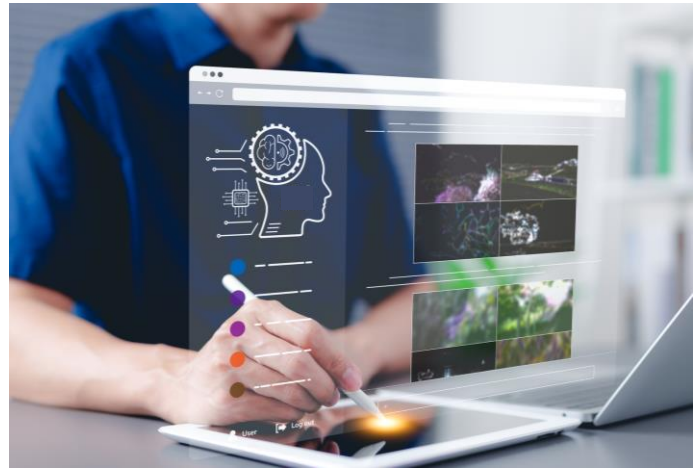
Challenges in dose selection in children <6 years

Ontogeny

Quantitative information essential to account for age-related changes in physiology, organ function and drug disposition

Patient centricity and operational feasibility

Sparse PK Sampling
Small blood volumes
Small sample sizes



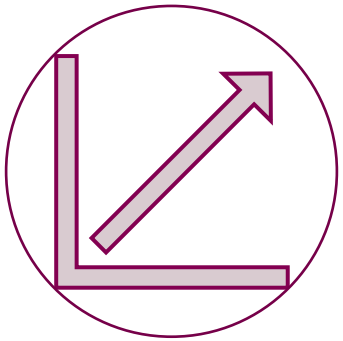
Data Limitations

Model-informed drug development supports practical, evidence-based dosing decisions

Framework for pediatric dose prediction in Industry

1. Pediatric strategy and initial pediatric dose predictions for PIP and iPSP using PBPK modelling

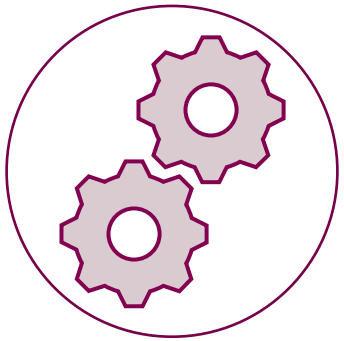
Adult Phase 2 and Phase 3 studies with adolescent patients to characterise PK



2. Phase 1 to 3 population PK modelling investigates covariates

Exposure-response analyses for safety, efficacy and PD biomarkers

Define efficacy and safety extrapolation exposure (and PD) metrics, in accordance with **ICH E11A**



3. PBPK and/or population PK model predicts initial pediatric dose levels

Investigate predicted exposure across age and weight range

Sensitivity analyses investigate uncertainty. Simulate clinical trial to inform study design

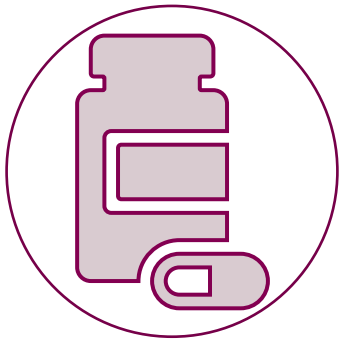
Update pediatric clinical trial protocol

4. Clinical pediatric PK study

Minimise blood sampling and volume

Characterise PK

Emerging pediatric data used to iteratively update model and refine dose predictions for lower age groups



5. Pediatric data used to update population PK and / or PBPK model

Exposure-response relationship investigated

If needed, inform design of further pediatric studies for safety and PD/efficacy

Pediatric **label dose** recommendations may be refined

Adult (and adolescent) → Pediatric

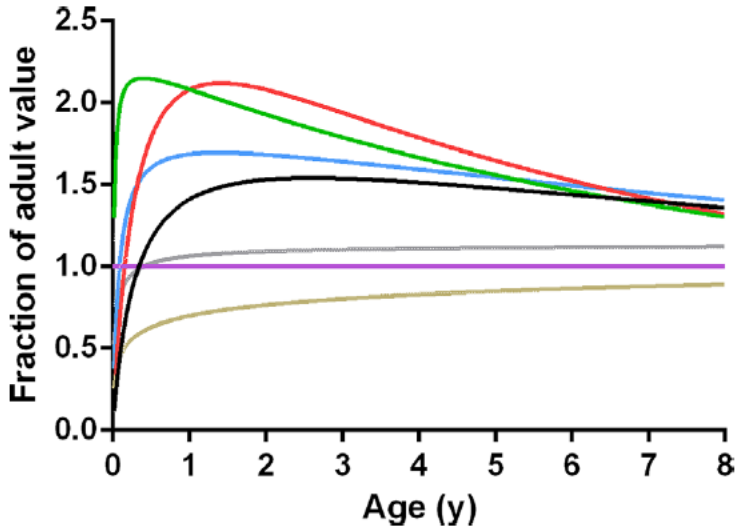
ICH E11A Pediatric Extrapolation Guidance for Industry https://www.fda.gov/media/161190/download

PIP: Pediatric investigation plan, iPSP: Initial Pediatric Study Plan; PBPK Physiologically Based Pharmacokinetic:; PK: Pharmacokinetic

Infants and children can have markedly different metabolic capacity compared to adolescents and adults

Phase 1 Cytochrome P450 (CYP)[1]

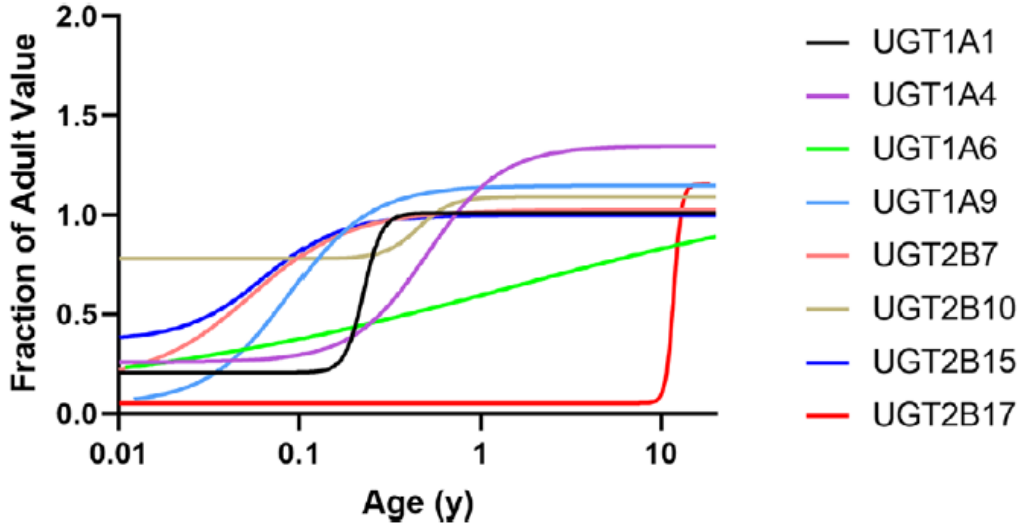
- CYP1A2 and 3A ontogeny clinically validated for PBPK modeling[2]



CYP1A2 (black), CYP2B6 (grey), CYP2D6 (purple), CYP2C9 (green), CYP2C19 (red), CYP2E1 (gold) and CYP3A (blue)

Phase 2 UGT[3]

- Limited understanding on the in vivo ontogeny of phase 2 enzymes



[1]Upreti VV, Wahlstrom JL. J Clin Pharmacol. 2016 Mar;56(3):266-83.

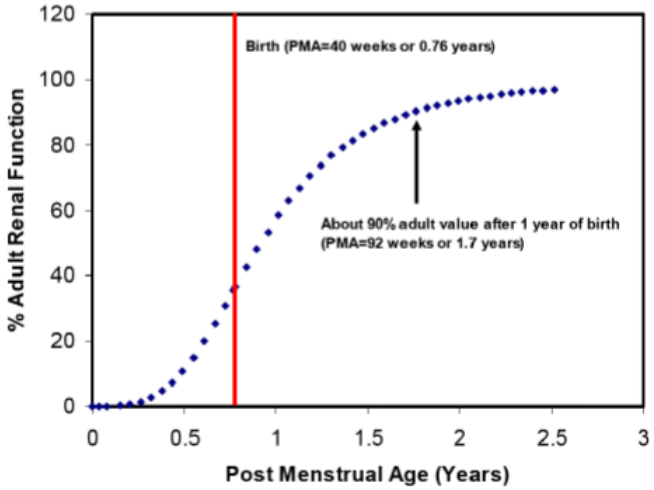
[2]Codaccioni M et al. J Clin Pharmacol. 2024 Sep;64(9):1083-1094.

[3]Farhan N, Dahal UP, Wahlstrom J. J Clin Pharmacol. 2024 Oct;64(10):1222-1235.

Glomerular filtration close to adult levels by 2 years of age. Drug transporters may influence drug disposition in children

Renal function[1]

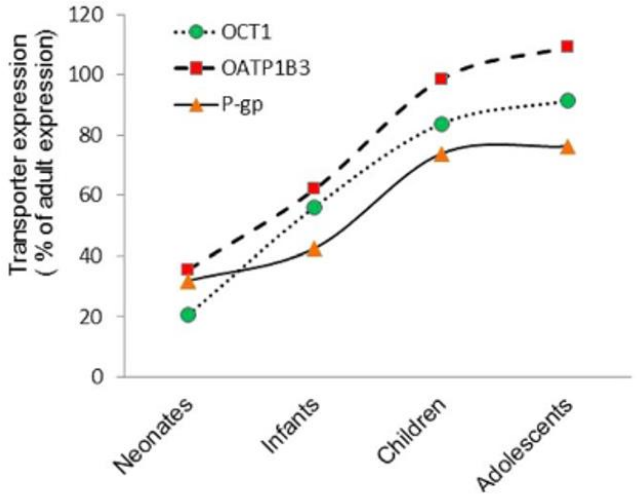
- Renal function maturation and allometry adequately estimate clearance for renally eliminated drugs



Rhodin maturation-based model[1]
eGFR (L/hr) =(WT/70)^0.75*(PMA^3.4/(PMA^3.4+47.7^3.4))*7.26

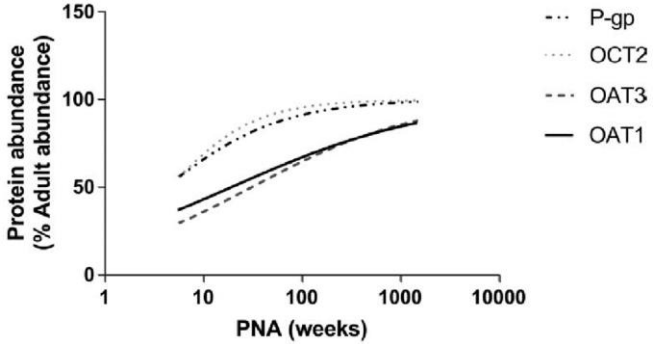
Hepatic Transporters[2]

- OCT1, OATP1B3, and P-gp lower in neonates and infants vs. older children. OATP2B1 and NTCP stable across age groups



Renal Transporters[3]

- P-gp, OCT2 and OATs increase with age
- No notable difference in BCRP from newborn to adults



For ACE inhibitors, e.g. lisinopril, absorption described by peptide carrier-mediated transport system[4]

[1]M. M. Rhodin, et al; Pediatr Nephrol (2009) 24:67–76. FDA/MCERSI Workshop 2019
[2]Prasad, B., et al. (2016), Clin. Pharmacol. Ther., 100: 362-370.
[3]Cheung, K.W.K., et al (2019), Clin. Pharmacol. Ther., 106: 1083-1092.
[4]Xie F., et al (2021) Br J Clin Pharmacol. 2021;87:1203–1214. https://doi.org/10.1111/bcp.14492

Monoclonal antibody modelling: allometric scaling and maturation function

Complex developmental processes

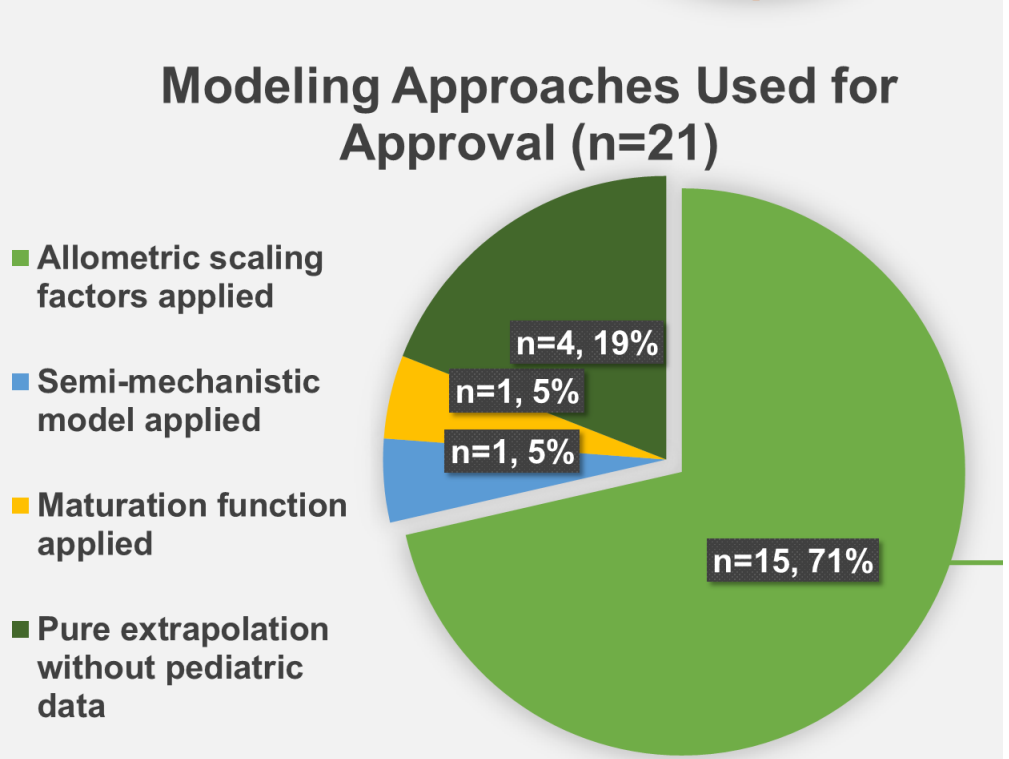
Distribution

- Larger extravascular distribution volumes expected in newborns and infants[1]
- Endogenous IgG, neonatal Fc receptor (FcRn) abundance and lymph flow change with age[2]

Elimination

- Target mediated drug disposition (TMDD): treatment specific and potential for maturation-related differences[2]
- Clearance in neonates and infants is better predicted using combined allometric scaling and maturation function vs. allometry alone[3]

Overview of modeling/strategies used for mAb approval 1998-2022[3]



[1] Zhang, X et al. (2024) Clin Pharmacol Ther, 115: 457-467. https://doi.org/10.1002/cpt.3056. Temrikar ZH., et al (2020) Paediatr Drugs. 2020 Apr;22(2):199-216. doi: 10.1007/s40272-020-00382-7

[2] Lim A. et al (2023) Pharmaceutics. May 20;15(5):1552. doi: 10.3390/pharmaceutics15051552. Pan X, et al. (2020) AAPS J. May 24;22(4):76. doi: 10.1208/s12248-020-00460-1.

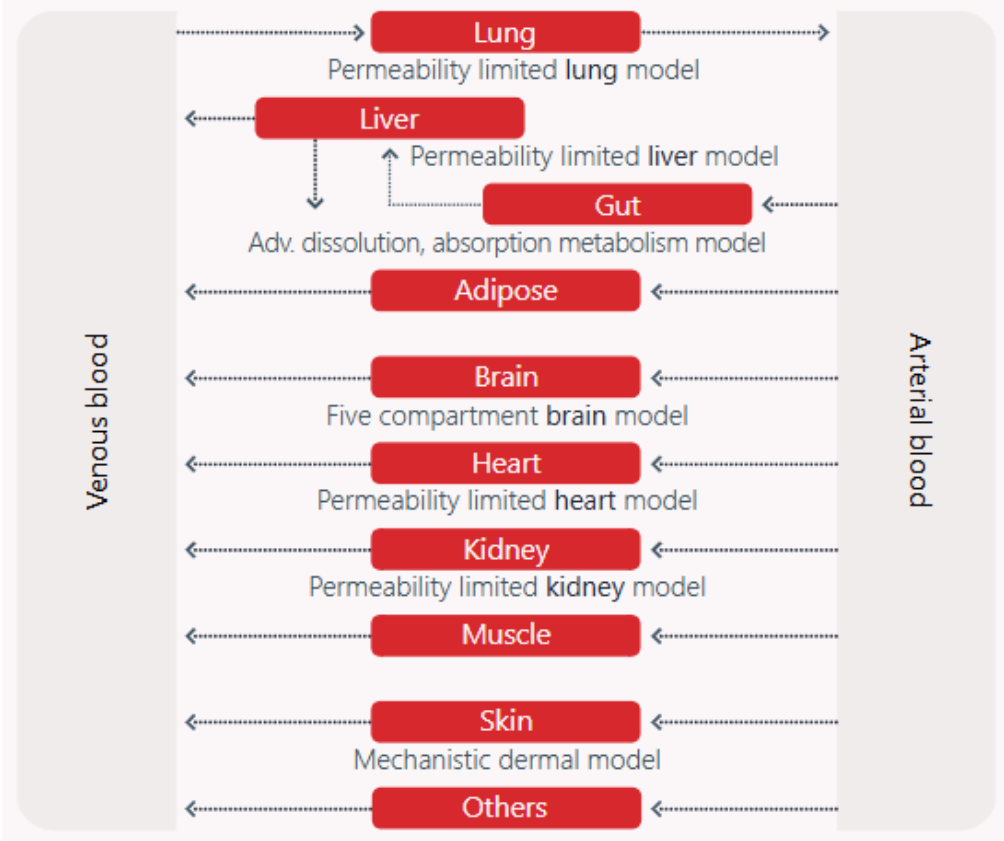
[3] Population PK Modeling of Monoclonal Antibody (mAbs) Drugs in Neonates and Infants (https://www.fda.gov/media/168957/download)

Physiologically-based PK model (PBPK) for pediatric dose prediction

PBPK model

- Developed prior to availability of pediatric data for initial pediatric dose predictions and optimisation[1]
- Describes concentration of drugs in relevant body tissues and organs. Integrates drug properties, physiology, and physiology/organ maturation
- Mechanistic scaling for **birth to <2 years range**. Accounts for maturation of the liver (CYP/UGT ontogeny) and rapid development of GFR during infancy
- Supports scenario testing across age and weight bands, formulations and clinical trial design simulations
  - e.g. evaluation of kidney disease in pediatric patients with hypertension[2], renal replacement therapy, cardiopulmonary bypass, drug-drug interactions and genetic polymorphisms

e.g. Simcyp® PBPK Simulator



[1]Zhou X, Dun J, Chen X, Xiang B, Dang Y, Cao D. CPT Pharmacometrics Syst Pharmacol. 2023 Jan;12(1):13-26. doi: 10.1002/psp4.12883. Epub 2022 Nov 20. PMID: 36330677; PMCID: PMC9835135.

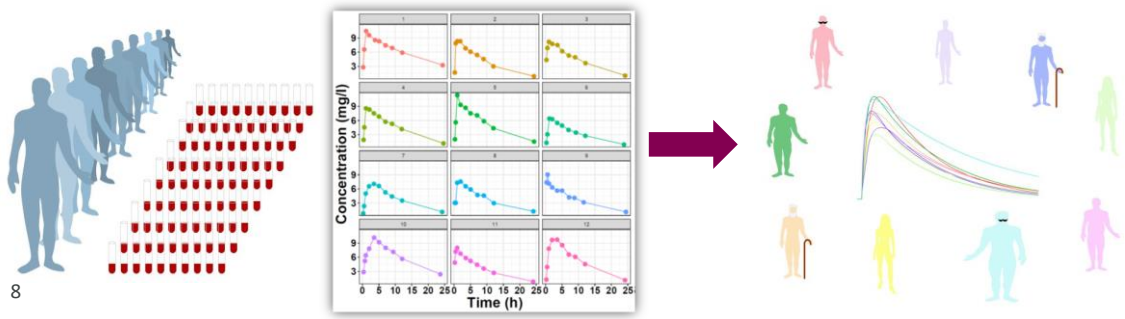
[2]Sandra L, et al. (2024). Br J Clin Pharmacol. 2024;90(2):504-515. doi:10.1111/bcp.15936

Population models for pediatric dose prediction

Population model

- Developed during Phase 1 to 3 using **adult and adolescent** PK data, multiple clinical trials and patients analysed
- One- or 2-compartmental PK model quantifies variability and relevant covariates such as race, age, weight and renal function (eGFR).
- **Exposure-response analyses** for safety, efficacy and PD biomarkers to support **adult and pediatric dose justification**

Phase 1



Phase 3

Pediatric dose prediction

- Alternative to PBPK models, for e.g.
  - Renally cleared small molecules[1]
  - Monoclonal antibodies
  - For similar treatment modalities, prior data and PopPK models can be leveraged and applied to new drugs
- Incorporate sparse PK sampling data
- Refine dose and exposure distributions across the population
- Informs future study design

[1]Sandra L, et al. (2024). Br J Clin Pharmacol. 2024;90(2):504-515. doi:10.1111/bcp.15936

2Stepanov O. et al (2024) PAGE Meeting Abstr 11135

Maximum allowable blood loss limits

European Commission's Guideline 2007[1]

Blood loss should not exceed:

- 1% of the total blood volume (TBV) at any single visit and
- 3% of the TBV during a period of 4 weeks

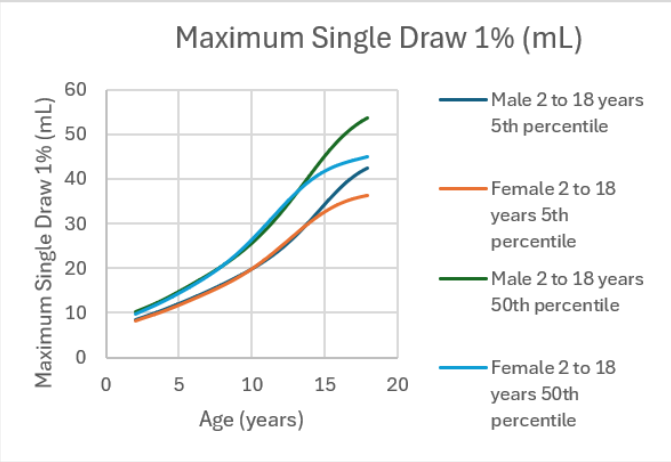
Estimated TBV: 80-90 mL/kg body weight

FDA does not define a limit

- US Local Institutional Review Boards and ethics committees enforce limits
- Generally, should not exceed:
  - 3% of TBV within 24 hour[2] and
  - 10% of TBV over 4 to 8-weeks

European Commission's Guideline Example

- 8 mL maximum blood loss for 2-year-old girl on 5th weight-for-age percentile at single visit[3]

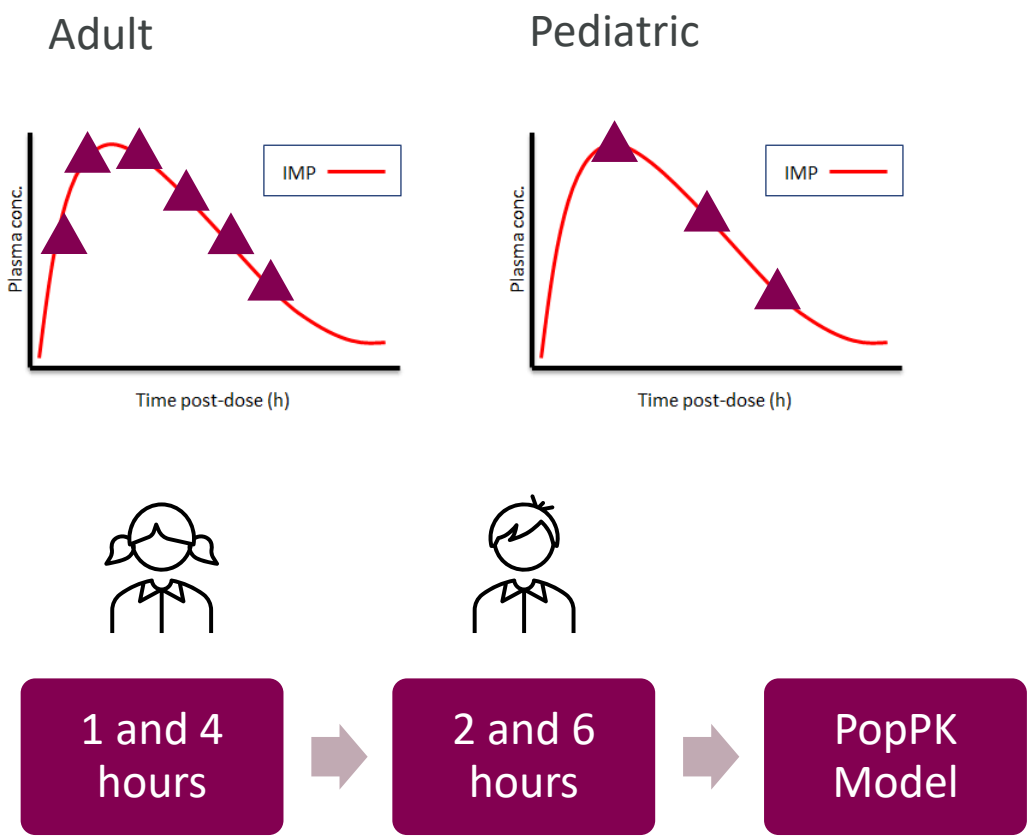


[1]European Commission's (EC) guideline Ethical considerations for clinical trials on medicinal products with the paediatric population. https://health.ec.europa.eu/document/download/d721d6cb-687a-477f-b40f-8c7922e9ec9a_ena532-3b8dc2ba6820_en

[2]Peplow C et al (2018) Acta Paediatrica Volume 108, Issue 5 pp. 940-944 Blood draws up to 3% of blood volume in clinical trials are safe in children. https://doi.org/10.1111/apa.14607

[3]CDC growth charts were used for children age 2 to 18 years https://www.cdc.gov/growthcharts

Strategic sampling: maximizing information, minimizing burden



- Minimize total samples by targeting key PK phases (e.g. Cmax, Ctrough, terminal phase)
- Clinical trial simulations incorporate prior adult data and the proposed sparse sampling schedule into hundreds of virtual trial replicates to mathematically prove operationally feasible cohorts (e.g., 8 to 12 children per weight band) will successfully hit precision targets for key parameters like clearance and volume
- Staggered sampling allow sparse data from multiple participants to be pooled into a robust PopPK model, minimising burden on any individual child

[1]ICH E11A Pediatric Extrapolation Guidance for Industry https://www.fda.gov/media/161190/download

[2]Wang Y., et al (2012) J Clin Pharmacol. 2012;52(10):1601-1606. doi: 10.1177/0091270011422812.

Practical Strategies for Pediatric PK Sampling

Microsampling

Transitioning to lower-volume assays significantly improves study practicality, e.g.:

- Volumetric absorptive microsampling (VAMS)
- Dried blood spots (DBS)

Combined Scheduling

- Combine PK sampling times with routine safety chemistry and hematology draws to reduce the number of needle sticks and clinical interventions

Logistics

- The constraint: Lower sample volumes mean back-up samples are often unavailable
- The solution: Mandate separate, staggered sample shipments to mitigate the risk of accidental loss during transit

Integrated Strategy: Practical Industry Recommendations

Start with the Clinical Question

- Define the disease, target population, and response first. Based on data availability and modality, select the most appropriate modeling framework (e.g., PBPK vs. PopPK) to propose initial doses.

Plan Holistically

- Design the dose, sparse sampling schedule, and assay volume limits simultaneously to ensure strict clinical and operational feasibility.

Simulate & Justify

- Use clinical trial simulations to justify the sample size by satisfying two distinct goals: achieving adequate precision for parameter estimation and demonstrating a high probability of meeting PK extrapolation targets.

Analyze & Refine

- Treat dose prediction as dynamic. Integrate emerging pediatric PK data into the population model to continually confirm and refine the strategy.

Thank you.

Successful pediatric drug development requires integrating sophisticated mathematical modeling with practical, patient-centric clinical execution

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