Accuracy of plasma clearance scaling from adults to children using pathway-specific covariate models: A systematic investigation using a physiologically-based pharmacokinetic workflow

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Introduction

Pathway-specific covariate model (PSCM) is a simple method to scale plasma clearance (CLp) across the pediatric population (Fig.1) [1,2], allowing for accelerated development of pediatric dose recommendations. PSCM describes CLp changes with bodyweight (e.g.: bodyweight dependent exponent) and/or age (e.g.: allometric scaling using a fixed exponent of 0.75 + maturation function).

Research question

Which conditions allow for accurate PSCM-based CLp scaling from adult to paediatric patients for drugs metabolized by one or several isoenzymes?

Methodology

A PBPK simulation workflow was developed in R (Fig.2), investigating the impact of all possible combinations of 5 variables on PSCM accuracy:

- postnatal age (AGE), range 1 day to 15 years
- drug properties of the model drug (M) (n= 37,800)
- drug properties of the test drug (T) (n= 37,800)
- isoenzyme A (I_A), for which PSCM between-drug extrapolation is performed (n=15)
- isoenzymes B (I_B), responsible for the remaining drug CLp (n=15)

Drugs metabolized by two isoenzymes (I_A and I_B) were defined by their fraction metabolized by I_A in adults (fm_adults).

PSCM-based CLp predictions were considered accurate when their absolute difference from the 'true' CLp was <30%.

Variables best discriminating between accurate and inaccurate PSCM-based CLp predictions were defined.

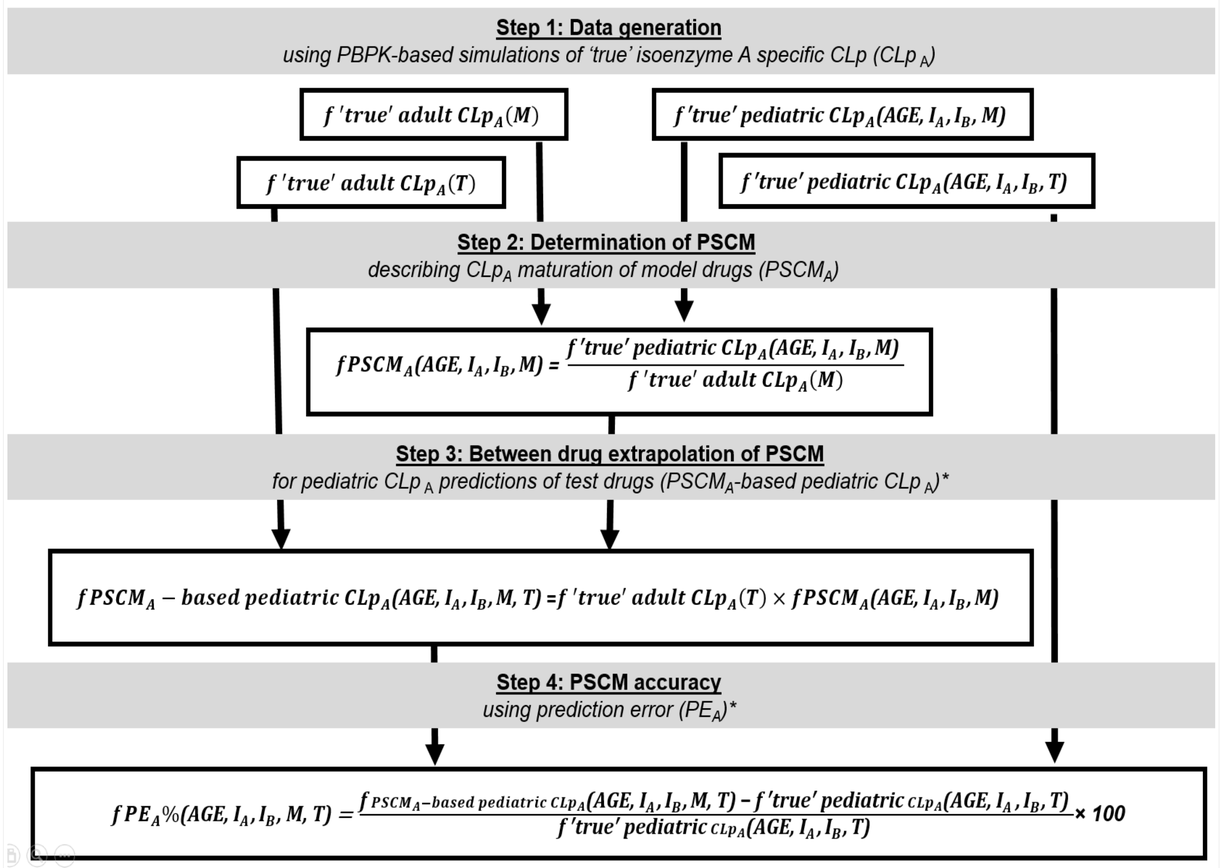

Fig. 2 *PBPK simulation workflow. Subscript A indicates isoenzyme A. * Indicates steps for which M and T bind to the same plasma protein. Investigated I_A and I_B were: CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C18_19, CYP2D6, CYP2E1, CYP3A4, UGT1A1, UGT1A4, UGT1A6, UGT1A9, UGT2B7 and SULT1A1.*

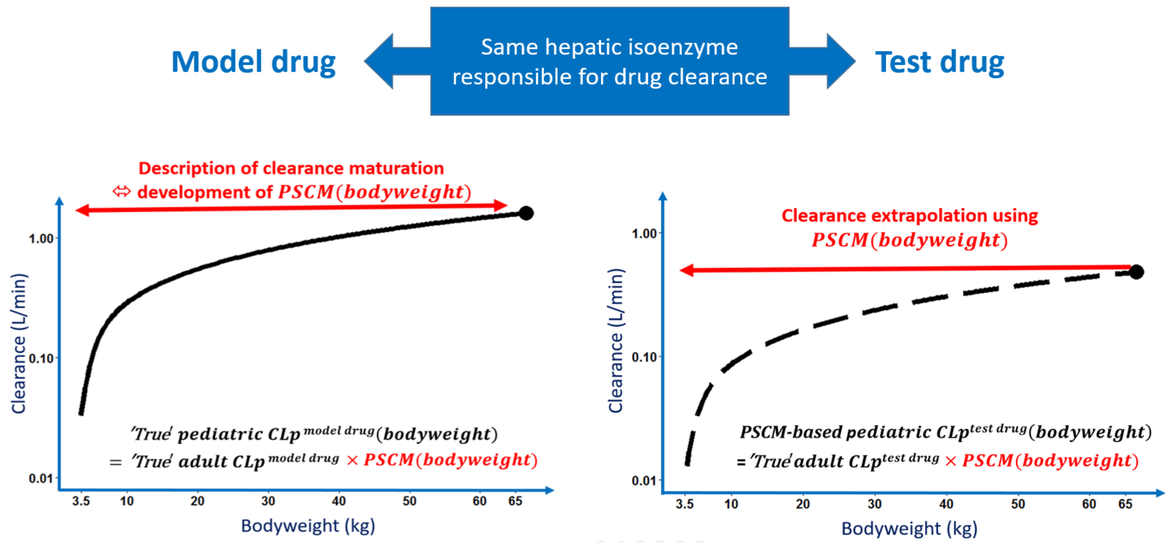

Fig. 1 *Between-drug extrapolation principles for PSCM-based CLp scaling from adults to children. CLp either represents total or isoenzyme-specific CLp for drugs metabolized by one or several hepatic isoenzymes respectively.*

Results

- For albumin bound drugs and all investigated isoenzymes, PSCM applicability increases with decreased extraction ratio (ER) and increased fm_adults of the model and test drugs (see Fig.3).
- For AGP bound drugs, PSCM generally led to inaccurate CLp predictions.

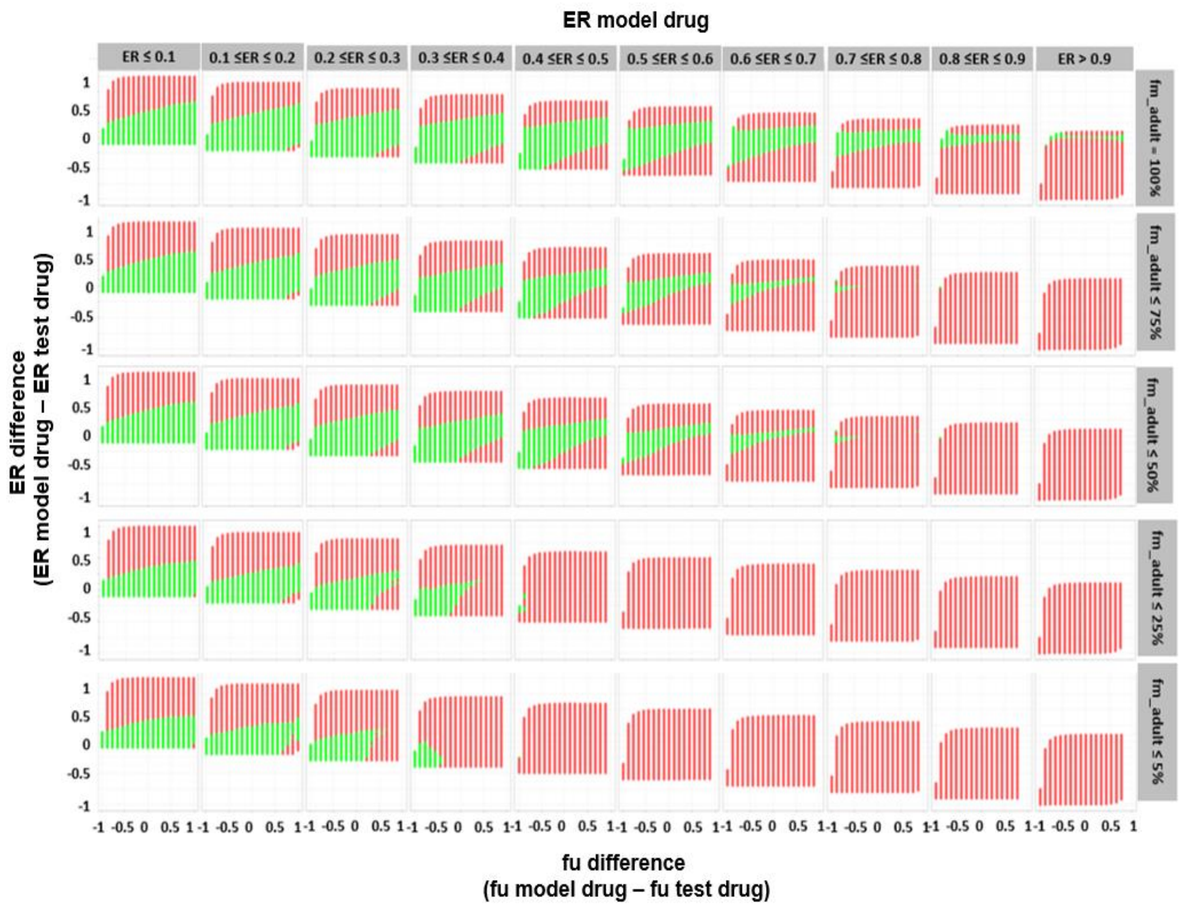

Fig. 3 *Relationship between drug properties and accuracy of PSCM-based CLp predictions for drugs bound to albumin and metabolized by CYP1A2.*
Predictions accurate for all ages (green) or inaccurate for at least one age (red).

Conclusions and Perspectives

PSCM only accurately scales CLp for specific combinations of model drug and test drug properties. Specifically, PSCM is mostly applicable to test and model drugs binding to albumin with a low or intermediate ER, which are predominantly metabolized by 1 isoenzyme.

References: [1] E. H. J. Krekels, CPT PSP. 2012;1(October):e9 ;[2] E. H. J. Krekels, CPT PSP 2012;1(October):e10