

# Physiology-based Versus Allometric Scaling Of Clearance In Children: A Comparison

Andrea N. Edginton <sup>1)</sup> & Stefan Willmann <sup>1)</sup>

<sup>1)</sup> Bayer Technology Services GmbH, Process Technology, Competence Centre Systems Biology, D-51368 Leverkusen, Germany

## INTRODUCTION

- Scaling of clearance to children is a prerequisite for the prediction of pharmacokinetics in children
- Allometric scaling is the most common method but has limited use in very young children
- Physiology-based scaling is more difficult but has been shown to predict clearance in children of all ages
- Objective:** Compare the two clearance scaling methods and determine if the age below which the allometric equation is no longer appropriate, is dependent on the major clearance pathway of the drug

## METHODS

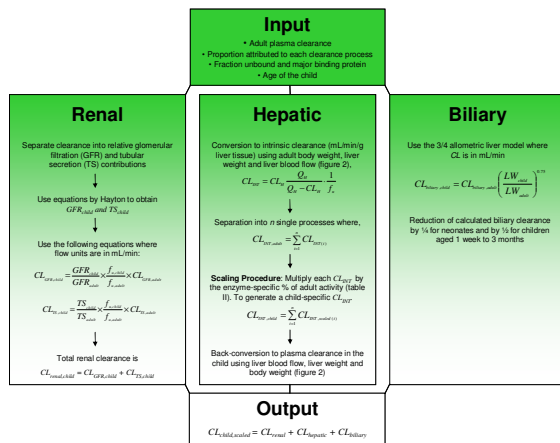
- Age-dependent clearance values were predicted using both the allometric equation and the physiology based method for a set of 15 drugs, eliminated via different routes (renal, hepatic via CYP3A4, CYP1A2, and UGT2B7)

### Allometric Approach

Uses the ratio of the child's body weight ( $BW_{child}$ ) to that of adults ( $BW_{adult}$ ) to convert total clearance in an adult ( $CL_{adult}$ ) to total clearance in a child ( $CL_{child}$  in L/h) as in the following equation:

$$CL_{child} = CL_{adult} \times \left( \frac{BW_{child}}{BW_{adult}} \right)^{0.75}$$

### Physiology-Based Approach <sup>[1]</sup>



- For each method, the predicted/observed clearance ratio was calculated and plotted against age.
- A visual assessment was made to determine the appropriateness of each method and if they were process specific

## RESULTS

### Comparison of Methods

- Allometric equation consistently overpredicted clearance in children under the age of about one year. Above, at least, an age of 4, the allometric approach is appropriate (Figure 2).
- The physiology-based method accurately predicted clearance in children of all ages except premature neonates.

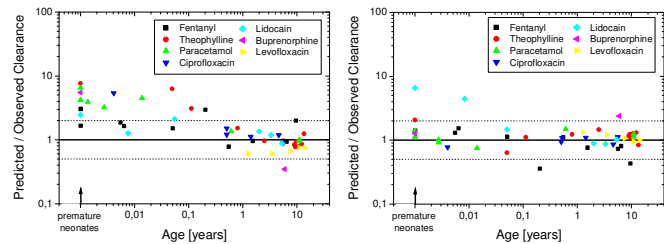


Figure 3. Predicted/observed clearance ratios vs. age using the allometric (A) and physiology-based (B) approach. The solid line indicates a perfect match of predicted and observed values.

### Process-Specific Differences

- The extent of the overprediction appears to be process specific (e.g. about 10x for CYP3A4 and only 2-3x for glomerular filtration) (Figure 3).
- The age at which the allometric approach accurately predicted clearance was process specific and followed the *in vitro* trends associated with the enzyme specific ontogeny.
  - CYP3A: fully developed by the age of 6 months
  - CYP1A2: the last enzyme to fully develop; between the ages of 1 to 15 years.
  - UGT2B7: fully developed by the age of 6 months
- The passive process of renal filtration was over predicted in children under 2 years of age and over predicted in children older than 2 years using the allometric approach.

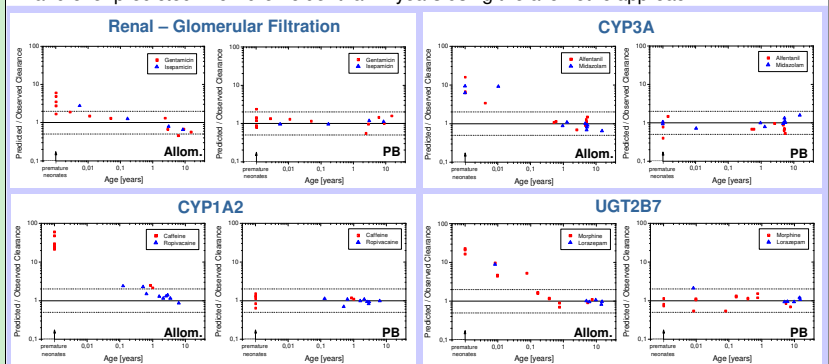


Figure 3. Predicted/observed clearance ratios vs. age using the allometric (Allom.) and physiology-based (PB) approach. The solid line indicates a perfect match of predicted and observed values.

## CONCLUSIONS

- The allometric method is biased (overprediction) when the maturity of the process driving clearance is not fully developed. The extent of bias is process-specific.
- For older children, the allometric equation provided an accurate means of scaling clearance for active clearance processes.
- Because the physiology-based approach takes into account the maturity of the clearance process, it was appropriate for children from term to 18 years of age.

[1] Edginton et al. A mechanistic approach to scaling clearance in children. *Clinical Pharmacokinetics*. In Press. (2006)

