Population PK Modeling of Monoclonal Antibody (mAbs) Drugs in Neonates and Infants

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Background

- Although they have been on the market for over a decade, for majority of mAbs with a pediatric indication, the dose recommendation for neonates and infants is generally extrapolated from older children and adult data given the challenges to conduct a study in the little kids.

Allometric Scaling Modeling Approach

- Predicts drug clearance for one population based on data from another.
- Takes morphologic characteristics and body size into account.
- Body size effects alone do not adequately explain changes in drug disposition due to maturation of organ, tissues, enzyme, and transporter systems in neonates and infants.

Maturation Function

- Additional considerations for age effects as a function of maturation on drug PK for this subpopulation (infants and neonates)

Objectives

- Collect PK data from the database of mAbs approved in pediatric patients.
- Explore PK parameter changes and maturation processes for pediatric patients.
- Conduct PopPK modeling and simulation to evaluate prediction accuracy of maturation functions in young pediatric patients (infants and neonates).
- Assess the impact of different modeling strategies to dosing recommendations in pediatric patients.

Methods

- mAb PK data from clinical studies were collected and used for model development. The model was developed using a stepwise approach using NONMEM 7.4 :
  - ➢ A database for drugs approved in pediatric patients (DocuBridge system)
  - ➢ A compartment structural model with allometric scaling factors
  - ➢ The maturation function + estimated allometric scaling factors from datasets
  - ➢ Three age groups of patients:
    - ✓ infant group (0-2y)
    - ✓ pediatric group (0-17y)
    - ✓ entire study population
- **Maturation function:**
  - ➢ T_{CL}= maturation half-life for CL
  - ➢ Beta= the fractional change in CL for a typical full-term (40-week PAGE) infant
  - ➢ PAGE= combination of gestational age and postnatal age using an asymptotic-exponential model

$$TVCL = \theta_{CL} \times (\frac{WT_i}{70})^{0.75} \times (1 - (1 - \beta) \times exp^{(-(PAGE - \frac{40}{4.35}) \times (\frac{ln2}{T_{CL}}))}$$

$$TVV_C = \theta_{V_C} \times (\frac{WT_i}{70})^1$$

Where:

$$PAGE = AGE\ (months) + \frac{Gestational\ age\ (weeks)}{4.35(\frac{week}{month})}$$

Conclusions

- The developed nonlinear mixed-effect models can be used to characterize the population PK of mAbs in infant population and quantify the effects of individual covariates on variability of mAb PK.
- The approach of estimating the allometric scaling factors by datasets instead of fixing them to the standardized allometric scaling factors (0.75, 1) widely used in the pediatric modeling improved the model fitting.
- The developed model, which combined the description of clearance as functions of the maturation process and the allometric scaling better predicted exposures of mAbs in the neonate and infant population than allometric scaling alone for various dosing scenarios.

Disclaimer: The opinions expressed are those of the authors and should not be interpreted as the position of the US FDA.

Preliminary Results

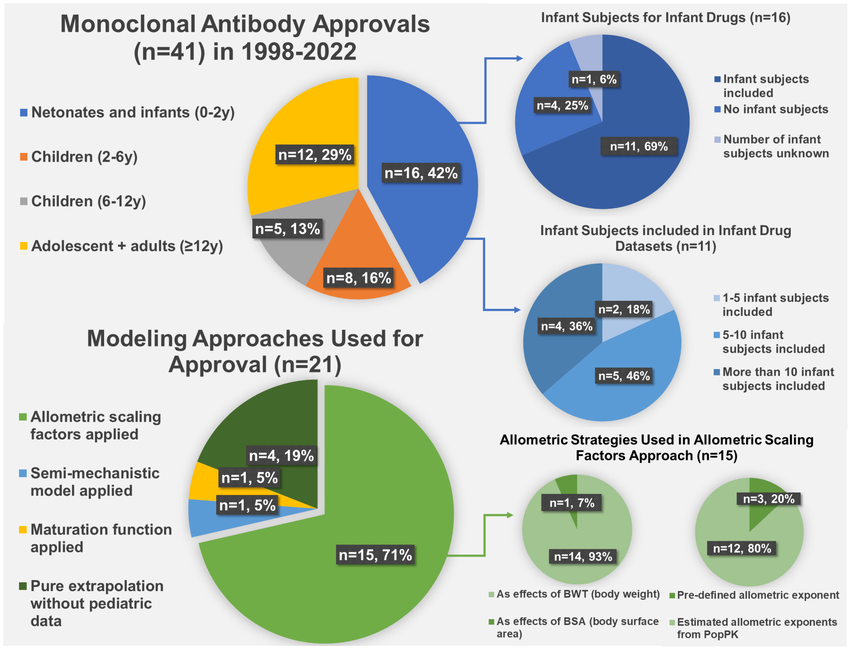

Figure 1: Overview of datasets and modeling approaches/strategies used for monoclonal antibody approvals from year 1998 to year 2022.

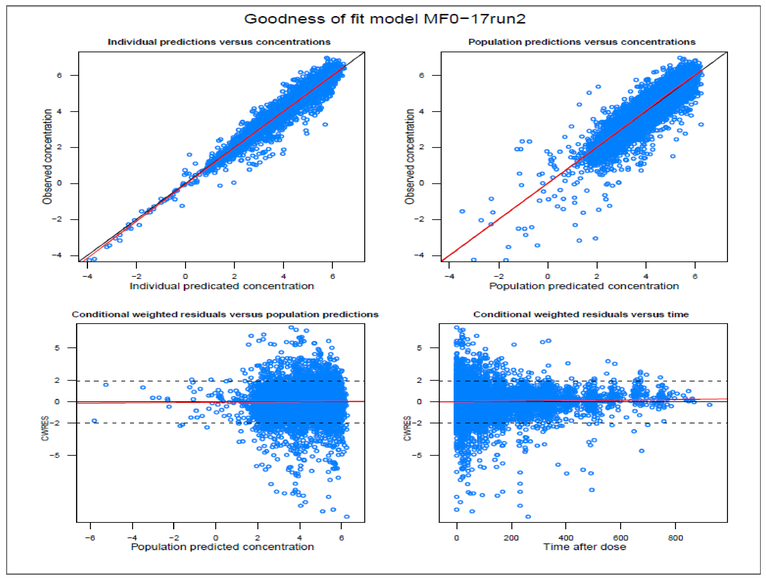

Figure 2: Example of Goodness of fit plots. The top two plots are observations against predictions (left: individual; right: population), the bottom two are residuals plots. maturation function model gives a better fitting. Because a significant reduction of objective function vale was observed along with a narrowed shape of predictions surrounding the unit line.

Monoclonal Antibody Approvals in 1998-2022	N	%
Total (pediatrics + adults)	41	
Netonates and infants (0-2y)	16	42.11
Children (2-6y)	8	15.79
Children (6-12y)	5	13.16
Adolescent + adults (≥12y)	12	28.95
Infant Subjects Info	**N=16 (Total infant drugs)**	
Infant subjects included	11	68.75
1-5 infant subjects included	2	18.18
5-10 infant subjects included	5	45.45
More than 10 infant subjects included	4	36.36
No infant subjects	4	25.00
Number of infant subjects unknown	1	6.25
Modeling Approach	**N=21**	
Allometric scaling factors applied	15	71.43
As effects of BWT (body weight)	14	93.33
As effects of BSA (body surface area)	1	6.67
Or		
Pre-defined allometric exponent	3	20.00
Estimated allometric exponents from PopPK	12	80.00
Semi-mechanistic model applied	1	4.76
Maturation function applied	1	4.76
Pure extrapolation without pediatric data	4	19.05

Table 1: Overview of datasets and modeling approaches/strategies used for monoclonal antibody approvals from year 1998 to year 2022. For applications without pediatric data, the dose recommendation for pediatrics was extrapolated from adult data.

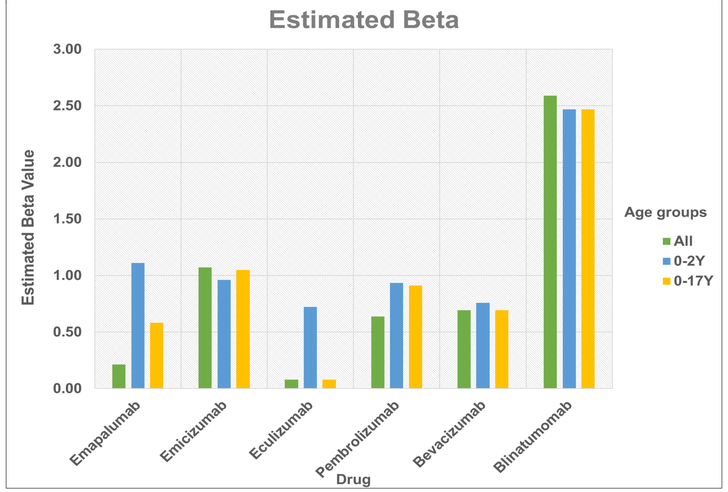

Figure 3: The distribution plot of estimated beta for six example monoclonal antibodies across the different age groups.

References

Population Pharmacokinetic Analysis of Palivizumab (BLA 103770) in Adults and Pediatric Subjects. Metrum Research Group, Jan. 10, 2011