Development of an interactive tool to explore paediatric doses and sample size for paediatric trials

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Objectives: To develop an interactive tool for: (1) exploration of paediatric dose levels that provide similar exposure as predicted for an adult reference population, and (2) calculation of sample size [1].

Methods: A virtual demographic database of subjects aged ≥1 month to ≤65 years was created based on the Continuous NHANES database [2] and the WHO weight-for-age tables for paediatrics aged ≤10 years [3]. Age-dependent maturation functions for renal and hepatic elimination pathways were implemented [4-5]. Required inputs include: a reference dose; clearance (CL), volume of distribution (Vc) and their variability in adult subjects. Typical CL values are simulated for adult and paediatric populations randomly sampled from the database; taking allometry, enzymatic and renal maturation into account.

Results: A bodyweight-based paediatric dose range is explored in the exposure simulations. Using the simulated CL values, AUCs are calculated at each dose level as: AUC=Dose/CL. For each paediatric age group, the bodyweight-based dose-level best matching the exposure at the reference dose in adults is determined. The percentage of paediatric subjects with exposures falling within the 95% prediction interval of the adult exposure is used as the decision criterion (Figure 1).

The paediatric PK sample size is determined as the minimum number of subjects to achieve “a 95% confidence interval within 60% and 140% of the geometric mean estimate of CL and Vc for the drug in each paediatric group with at least 80% power” [1]. Virtual paediatric PK trials for each age group are generated by sampling from the database. Individual CL and Vc values are then simulated. The power to fulfil the FDA requirement is explored for each sample size across all simulated trials.

Conclusions: An interactive tool was developed to facilitate paediatric drug development.

References: