Application of a Framework Qualifying Fit-for-Purpose Physiological Models to Drug Discovery and Development

Karim Azer*, Jeffrey R. Sachs*, Carolyn R. Cho, Thomas Kerbusch¹, Antonio Cabal, Christopher R. Gibson, Sandra Allerheiligen

PPDM-QP2, Merck & Co., Inc., Currently ¹Sanofi Pharmaceuticals, and ²Quantitative Solutions.

Objectives: Physiological models are frequently applied with pipeline. In addition to other quality management systems, it was essential to develop consistent, reliable processes for ensuring models’ scientific quality. The processes were used on a physiologically-based pharmacokinetic (PBPK) model for montelukast PK predictions in order to foster support for using PBPK predictions in future decision-making.

Methods: The modeling process was carefully analysed through interviews and literature reviews, including collaborative and organizational steps, and broken into components (Figure). The components include: ► Communication strategy; ► Questions that the model will address; ► Decisions impacted; ► Model description including relation to questions; ► Assumptions required and their impact; ► Data required, used, variability, and limitations; ► Estimation of parameters, variability and uncertainty predictions, and risks.

These steps were used to investigate the ability of PBPK modeling of montelukast to predict PK in children from adult PK data and known physiological differences (e.g. body size and composition, enzyme ontogeny). The initial SIMCYP [2] model used only in vitro data for the known elimination pathways in adults (without fitting to observed PK data) to describe the overall central tendency and variability in the adult PK data. One parameter (hepatic clearance) was then calibrated using adult IV data. The model was then used to (retrospectively) predict adult PK profiles for oral dosing, and pediatric PK using enzyme-specific age-dependence.

Results: Adult and pediatric oral-dosing profiles were reasonably predicted (figure). PBPK modeling was accepted for decision-making in pediatric development (such as selecting doses for clinical trials).

Conclusions: Strategic application of a model qualification framework can impact quality and organizational acceptance of models: clear separation of the calibration and (two) data qualification steps (and communicating the intent) was essential to proper model formulation and successful adoption. PBPK models can inform pediatric development.

References: