Children are physiologically different from adults in ways that can affect drug metabolism and effects. Nonetheless, most medicines are currently prescribed to children in an "off-label" manner, with dosages extrapolated from adult data through body weight and surface areas calculation. This lack of PK information can result in adverse effects due to high doses, or suboptimal benefit due to inadequate dosages. PK assessment in neonates is difficult because:

- PK analysis requires frequent blood draws
- Standard drug data are not available
- Standard assay of radio-labeled drugs can result in significant exposure

Accelerator Mass Spectrometry (AMS) is a technology that provides accurate PK measurement with much lower sample volume and exposure. A recent clinical trial sought to establish AMS as a tool for assessing drug PK in neonates.

PhysioPD Analysis

The PhysioPD modeling effort focused on developing a physiological model of bile acid transport which could be linked to other PK models. The model was built and validated for use in accordance with Rosak Model qualification method (Figure 6). Research objectives, as recorded in an MDD document that accompanies the model.

PK Analysis

Mixed effect modeling identified a 2-compartment model as the best fit of the data, as can be seen in various diagnostic graphs. Furthermore, there was a generally good agreement with micro-compartmental analysis (NCA; not shown). (Figure 1) resulted in apparent CL and V values. Similar to the NCA results, large inter-subject variability in the PK parameters identified.

PhysioPD Conclusions

- A 2-compartment model fitted the data best.
- AMS can be used to study complicated PK in neonates.

Insights from PhysioPD Analysis

- Contrary to dogma, bile acid recycling and secretion under feeding.
- Flux of bile acids into systemic circulation must be substantially to match drug appearance rates in plasma.
- Secretion rate out of gall bladder under parenteral feeding (i.e., no food in GI tract) must be substantially to match the recycling rate (see Figure 12).
- Subject plasma profiles suggest variability in multiple transport steps.
- Suggest variability in distribution across compartments, which may have implications for drug efficacy.
- Relative flux into the GI tract vs. plasma to liver shows the initial peak subject. Subsequently, peak values have relatively flat plasma to liver transport while subject body weight
- Known polymorphisms may explain this variability (Figure 10).
- A best estimate for the uptake/release rate constant greater than what is compatible with reported synthesis rates and equilibrium posture.
- May point to differences between neonate and adult subjects, fed and unfed subjects, specific-ethnic regulation or other mechanisms.