Non-compartmental Analysis vs. Target Mediated Drug Disposition Modeling: Predictive Accuracy in Interspecies Scaling of Interferon Beta-1a

E. Offman, A. N. Edginton
University of Waterloo

**Purpose**
Estimating the pharmacokinetics (PK) of therapeutic biologics using non-compartmental (NCA) methods can result in poor predictions, particularly for volume (V). Employing population approaches (PPK) for estimating V may improve the prediction accuracy when combined with single-species scaling (SSS) methods.

The objective of this research was to test the hypothesis that PPK of a single nonhuman primate species will improve the prediction accuracy of V/F and CL/F from a subcutaneously (SC) administered biologic (interferon beta-1a, IFN) compared to parameters derived by NCA. Fold-error (FE) within the range of 0.7-1.3 was considered as a reasonable prediction.

**Methods**
PK parameters estimated by NCA were derived from four rhesus monkeys administered a single SC of IFN 35 mg/kg. Scaling to human values was performed using single-species allometry with varying fixed exponents; correction for liver blood flow (LBF) and Dedrick plots varying the exponent for CL/F. FE was calculated by comparing the mean scaled values to mean observed NCA-derived PK following administration of a single 88 mcg SC dose to 128 healthy males and female volunteers.

Concentration data for both species were also fitted to a target-mediated drug disposition PPK model. A population of 100 monkeys was simulated from the final model and prediction accuracy was calculated based on the mean of the simulated dataset.

**Results**
As the exponent varied from 0.75-1, FE from mean NCA-derived values ranged from 0.10-0.29 and 0.99-2.84 for V/F and CL/F. Scaling mean V/F and CL/F by LBF resulted in FE of 0.09 and 0.64 for V/F and CL/F. Simplified Dedrick Plots varying the exponent for CL/F between 0.75-0.85 and fixing the V/F exponent at 1, resulted in reasonable prediction accuracy for CL/F however poor prediction for V/F. In contrast, SSS of V/F derived from PPK and an exponent of 1 resulted in FE of 0.94. CL/F scaled with good accuracy when the exponent ranged from 0.75-0.85.

**Conclusion**
NCA-derived V/F scaled poorly following single-SC dose of IFN to monkeys, whereas PPK-derived V/F scaled with high prediction accuracy with an exponent of 1. CL/F scaled reasonably well regardless of method employed provided the exponent ranged from 0.75-0.85.