Review on Prospective Predictions of Human Pharmacokinetics for Sixteen Novartis Compounds
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Purpose
Quantitative predictions of human pharmacokinetics and concentration-time profiles from in vitro and preclinical in vivo data are critical in drug discovery and development to determine first-in-human dosing. The aims of the present study were to evaluate the prospective prediction accuracy of human pharmacokinetics for 16 Novartis compounds by using the highly recommended methodologies reported by the publications from the PhRMA CPCDC initiative, and provide further insight based on our experiences.

Methods
A dataset composed of sixteen small molecular compounds developed at Novartis Pharmaceutical Corporations were employed in this analysis. Among them, three, nine, two and two compounds were classified as BCS I, II, III and IV, respectively. The plasma clearance (CL) was predicted by the allometric scaling method with the rule of exponent (ROE), fu corrected intercept method (FCIM) or in vitro-in vivo extrapolation (IVIVE) method. The volume of distribution at steady state (Vss) was predicted by either Oie-Tozer approach or allometric scaling methods. Human intravenous profiles were obtained by superimposition of the preclinical data using Wajima formulas, and oral profiles were simulated either with the physiologically based oral absorption and pharmacokinetic model of GastroPlusTM or by simple combination of predicted intravenous pharmacokinetics with the average bioavailability (F) and absorption rate constant (ka) of the preclinical species. The key pharmacokinetic parameters evaluated here were the maximum plasma concentration (Cmax), the area under the plasma concentration-time curve (AUC), CL/F and Vss/F.

Results
Eleven out of sixteen (69%) compounds showed relatively good prediction results, either with all four parameters (Cmax, AUC, CL/F, Vss/F) having predicted values within 2-fold of observed values, or three parameters within 2-fold of observed values and the other one parameter was only slightly off.

Conclusion
We demonstrated that the PhRMA CPCDC initiative recommended methodologies can give very good prediction accuracy of human pharmacokinetic profiles based on this dataset. Significant improvement could be achieved by comprehensive analysis of all the ADME properties specific to a particular compound to proactively address the challenges such as nonlinearity, species disconnection and prediction confidence.