A Model-Based Meta-Analysis (MBMA) of Pharmacokinetic Drug Interactions: Run One, Know Everything

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Objectives: Pharmacokinetic drug-drug interactions (DDI) are important to consider during clinical development to ensure safety both for the current drug and for concomitant medications. DDI studies are usually conducted during Phase 1 or 2 for commonly co-administered therapies and during Phase 3 for reference and narrow-therapeutic-index therapies [0]. PBPK models are accepted in FDA guidance for prediction of CYP3A interactions and for guidance on other CYP interactions, but limitations remain with PBPK for other interactions [0]. The objective of this work is to develop a MBMA for DDI to predict many DDI from a small set of clinical results.

Methods: A MBMA database was built from literature using reference compounds for CYP3A substrates and inhibitors. The database included all relevant information on study and population characteristics, dosing (including relative timing of dose, duration of dosing, and enabling analysis of cocktail interaction studies), and DDI results including point estimates and variability. The MBMA then estimated drug- (and if applicable dose-) response for reference compounds to estimate the interactions for a reference substrates and inhibitors.

Results: A database was constructed with 45 references with 55 studies and 839 subjects including 48 drugs in 94 different combinations. The database allows examination of relative inhibition of CYP3A with various reference drugs, and it allows for model generation to predict drug interactions across a range of CYP3A inhibitors given limited clinical drug interaction data.

Conclusions: A DDI MBMA has been developed that predicts CYP3A substrate and inhibitor DDIs from a limited set of study results. The methods can be extended to predict other interaction types potentially including transporter interactions enabling improved predictions of DDI without requiring additional clinical studies. Future directions include prediction across multiple classes of interaction simultaneously.