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ARTICLE IN REVIEW:

Evaluating CYP2C-Mediated Drug-Drug Interactions: A Combined TruVivo® and PBPK Approach

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TITLE: Physiologically Based Pharmacokinetic Modeling to Assess Perpetrator and Victim Cytochrome P450 2C Induction Risk.[1]

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STUDY DESIGN: Integrated *in vitro–in silico* study

SUMMARY: Accurate preclinical prediction of cytochrome P450 2C (CYP2C) induction-mediated drug–drug interactions (DDIs) remain challenging due to limited induction response in traditional *in vitro* systems and scarce clinical data. This study aimed to evaluate the integration of *in vitro* CYP2C induction data from TruVivo, a human 2D+ hepatic system, into physiologically based pharmacokinetic (PBPK) modeling to improve quantitative DDI risk assessment.

In vitro induction parameters for CYP2C8, CYP2C9, and CYP2C19 were measured using rifampicin, efavirenz, carbamazepine, and apalutamide and incorporated along with intrinsic clearance (CL_{int}) of victim drugs into PBPK simulations of clinical pharmacokinetics with and without perpetrator co-administration. Predicted pharmacokinetics were compared with mechanistic static models (MSM) and observed clinical outcomes. PBPK models that included measured induction parameters and enzyme fractional metabolism (f_m) demonstrated improved prediction of victim drug exposure changes relative to MSM, achieving close alignment with observed clinical DDI data. These findings support PBPK modeling as a complementary approach for evaluating CYP2C induction risk in DDI assessment.

PBPK modeling improved quantitative prediction of CYP2C induction DDIs

By integrating *in vitro* induction parameters and enzyme fractional metabolism into PBPK models, quantitative predictions of victim drug exposure changes were achieved that correlated strongly with clinical observations. This contrasts with mechanistic static models, which accurately predicted CYP3A outcomes, but lacked similar precision for CYP2C enzymes.

TruVivo induction data provided relevant input for modeling

Induction parameters for CYP2C enzymes obtained from TruVivo enabled mechanistic incorporation into PBPK simulations. This approach better captured *in vitro* induction dynamics than traditional monolayer hepatocyte systems and supported improved translation to clinical outcomes.

Incorporating enzyme fractional metabolism alongside TruVivo induction parameters enhanced predictive fidelity

Combining enzyme-specific fractional metabolism (f_m) with TruVivo-derived induction parameters reduced over- and underprediction in CYP2C DDI simulations. This demonstrates the value of pairing high-quality *in vitro* induction data from TruVivo with drug-specific metabolic context to strengthen quantitative DDI risk assessment.

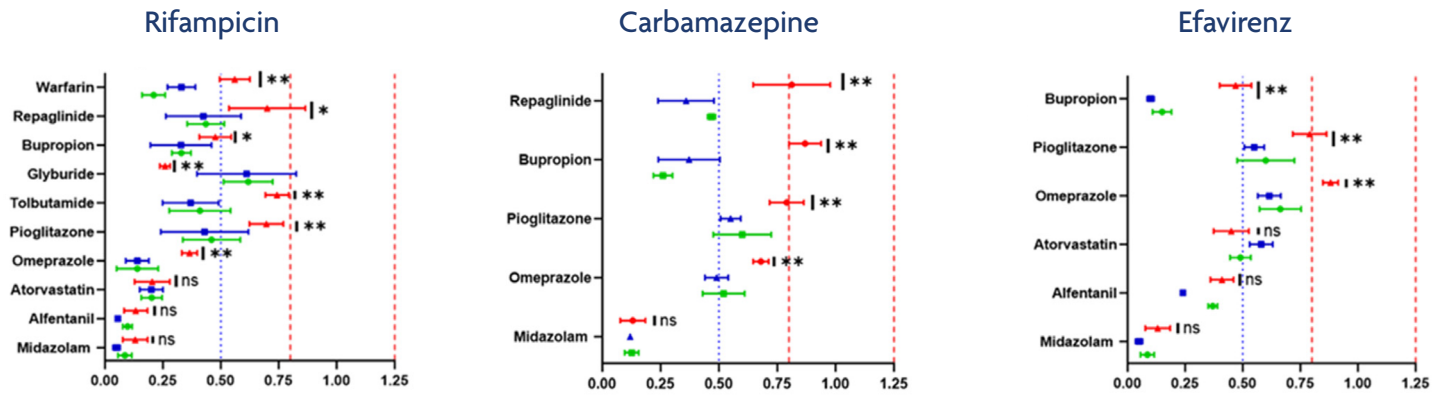

Figure 1. PBPK vs. static modeling predictions using TruVivo-derived CYP induction data. Graphs compare PBPK (green) and static model (red) predictions of victim-drug AUC ratios with observed clinical values (blue) following rifampicin (left), carbamazepine (middle), or efavirenz (right) treatment. PBPK simulations informed by TruVivo induction parameters more closely align with clinical outcomes, demonstrating improved prediction accuracy for CYP2C induction. Image reproduced from portions of Figure 3 of Slavsky *et al.* with permission under an open access license.[1]

References

Marina Slavsky, Aniruddha Sunil Karve, and Niresh Hariparsad. (2025). Physiologically Based Pharmacokinetic Modeling to Assess Perpetrator and Victim Cytochrome P450 2C Induction Risk. *Pharmaceutics*, 17, 1085. DOI: 10.3390/pharmaceutics17081085.