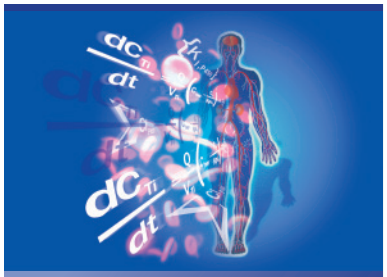
cyprotex AN EVOTEC COMPANY

***In Silico* Prediction**

DDI-Fusion: Human DDI Predictor

Background Information



'A tool for integrating *in vitro* ADME data with chemical structure to predict human DDI.'

- Predicts human DDI (midazolam AUCR) using a proprietary algorithm that takes *in vitro* CYP interaction data (reversible inhibition, time dependent inhibition and induction) and chemical structure as inputs.
- Customisable for alternative CYP3A4 substrates or alternative CYP enzymes.
- chemPK™ v2 predicts key human pharmacokinetic parameters directly from structure. The predicted systemic and gut wall C_{max} values are used as inputs for DDI-Fusion.
- DDI-Fusion has several advantages over the regulatory mechanistic static model in that:
  - it uses a data-driven optimisation approach requiring fewer assumptions
  - human C_{max} is predicted so no clinical *in vivo* data are required
- Provides early stage filter for directing chemistry and prioritising screening.
- Superior approach which uses PBPK model optimised from human clinical (*in vivo*) CYP3A4 data.

DDI-Fusion Input Requirements

- Structural information
  - Chemical structure, e.g., SMILES, mol or sdf
  - Net charge at pH 7.4, calculable from pK_as
- Dosing information
  - Dosing regimen of perpetrator (dose, route frequency, duration)
- *In vitro* data
  - Reversible K_i or IC_{50}, TDI (K_I and k_{inact}) and induction (EC_{50} and E_{max}) parameters
  - Fraction unbound in plasma ($f_{u,p}$)

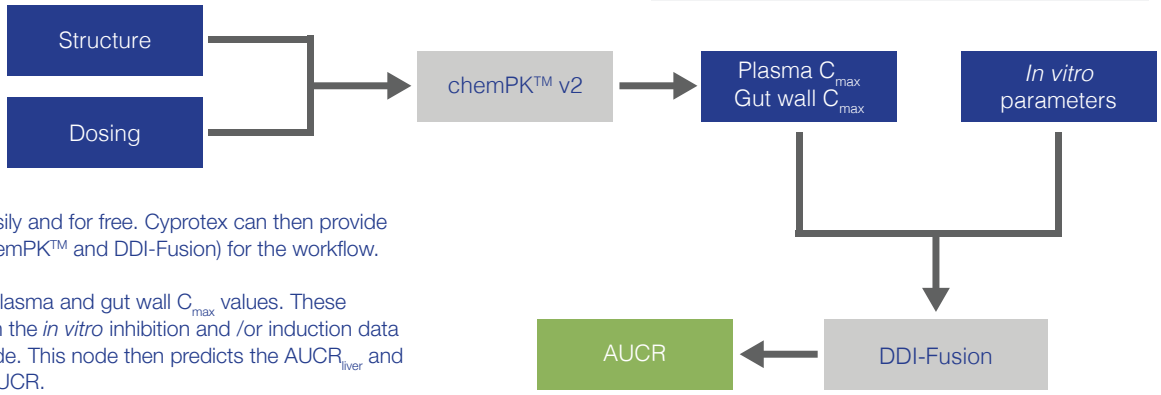
DDI-Fusion Data Delivery

Predicted AUCR of victim for oral delivery (plus liver and gut contributions)

How does it work?

DDI-Fusion integrates liver and gut PK data from chemPK™ with *in vitro* CYP interaction data in a KNIME workflow-based approach which executes the process illustrated in Figure 1.

Figure 1
DDI-Fusion workflow process.



KNIME can be downloaded easily and for free. Cyprotex can then provide the bespoke KNIME nodes (chemPK™ and DDI-Fusion) for the workflow.

Initially chemPK™ v2 predicts plasma and gut wall C_{max} values. These parameters are used along with the *in vitro* inhibition and /or induction data as inputs to the DDI-Fusion node. This node then predicts the $AUCR_{liver}$ and $AUCR_{gut}$ for estimation of the AUCR.

To find out more contact **enquiries@cyprotex.com**

Calculation of AUCR by DDI-Fusion

DDI-Fusion predicts AUCR of a co-administered victim drug (e.g., midazolam) in the presence of the perpetrator drug (test article).

$$AUCR = \frac{\text{AUC of victim in presence of perpetrator}}{\text{AUC of victim in absence of perpetrator}}$$

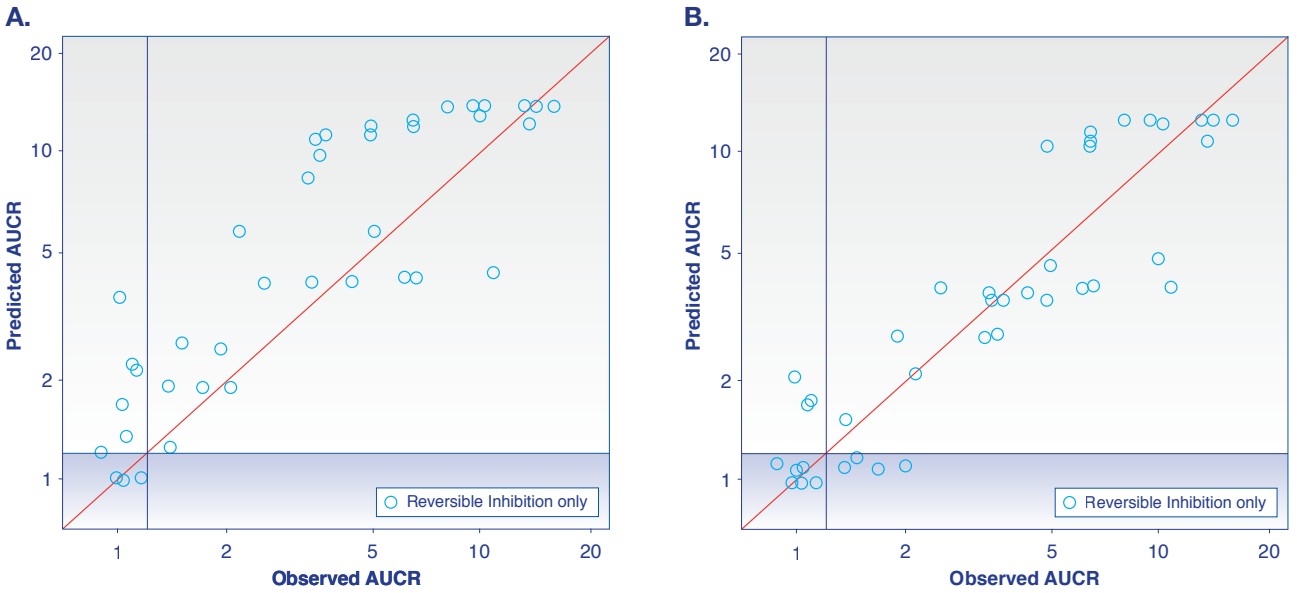
If inhibitory effects dominate, AUCR > 1
If induction effects dominate, AUCR < 1

Additionally, DDI-Fusion predicts the contributions of DDI in (i) the gut ($AUCR_{gut}$), and (ii) the liver ($AUCR_{liver}$).

$$AUCR_{total} = AUCR_{gut\ wall} \times AUCR_{liver}$$

Figure 2

Comparison of (a). the mechanistic static model as recommended by the regulatory authorities, and (b). Cyprotex's DDI-Fusion model for predicting AUCR of reversible CYP3A4 inhibition against midazolam.



The data illustrate how the regulatory mechanistic static model over-predicts AUCR for inhibition leading to false positives and possible unwanted compound attrition.

Table 1

Statistics comparing the regulatory mechanistic static model with Cyprotex's DDI-Fusion model.

	Regulatory Mechanistic Static Model	DDI-Fusion
R^2	0.63	0.70
RMSE	3.67	2.53
GMFE	1.58	1.36

We are looking for partners with whom we can further develop the DDI-Fusion model. If you would like to be involved then please get in touch.

Contact enquiries@cyprotex.com for a demonstration.