cyprotex AN EVOTEC COMPANY

In Silico **Physiological Modelling**

PK Prediction From *In Vitro* Data

Background Information

'A rapid screening service for integrating *in vitro* ADME data and structural information.'

- Cyprotex's human PK prediction service is a combined *in vitro/in silico* offering that has been developed to provide reliable prediction of human PK from a minimal set of tier 1 ADME data.
- Suitable for use in lead identification (LI) and lead optimisation (LO) stages of drug discovery.
- Predict pharmacokinetics (PK) for oral (po), intravenous (iv) bolus, or infusion regimens from the integration of ADME data and structural information.
- Plasma concentration-time profiles and summary PK parameters provided for maximum utility.
- No specialised staff required.
- No software licencing costs.
- Predictions within one working day of receipt of ADME data, if using Cyprotex *in vitro* ADME data package.
- Scales seamlessly from a single compound to hundreds of compounds, with no added delay

Protocol

Data Requirements

- Intrinsic clearance measured in either human liver microsomes or human hepatocytes.
- Fraction unbound in human plasma.
- Compound structure – as either SDF or SMILES file.
- Optional human blood to plasma ratio.
- Optional dose regimen.

Data Delivery

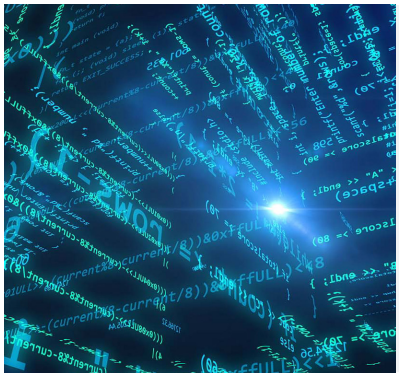
Predictions are delivered in an Excel workbook containing the following worksheet tabs:

- A summary sheet containing summary PK parameters for all combinations of compound and dose regimen simulated.
- A single sheet for each compound/dose combination, containing:
  - Plasma concentration-time profile data for 24 hours following final administration.
  - Linear plot of plasma concentration-time profile.
  - Semi-logarithmic plot of plasma concentration-time profile.

Predicted PK parameters and plasma profiles can be easily read into databases or modelling software for further manipulation. Plots can be immediately copied into presentations or documents, or formatted to suit specific presentation requirements.

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

A PBPK model is used to simulate human PK from *in vitro* ADME data and structural descriptors



Two options for using the service are available:

1. Send compounds for screening through Cyprotex's ADME assays (human plasma protein binding; human hepatocyte stability or microsomal stability; optional human blood to plasma ratio) as well as structures in SMILES or sdf file. Predictions will be returned within one working day of ADME data being finalised.

2. Send pre-generated data along with compound structures. Predictions will be returned within five working days of receipt of the data and structure package.

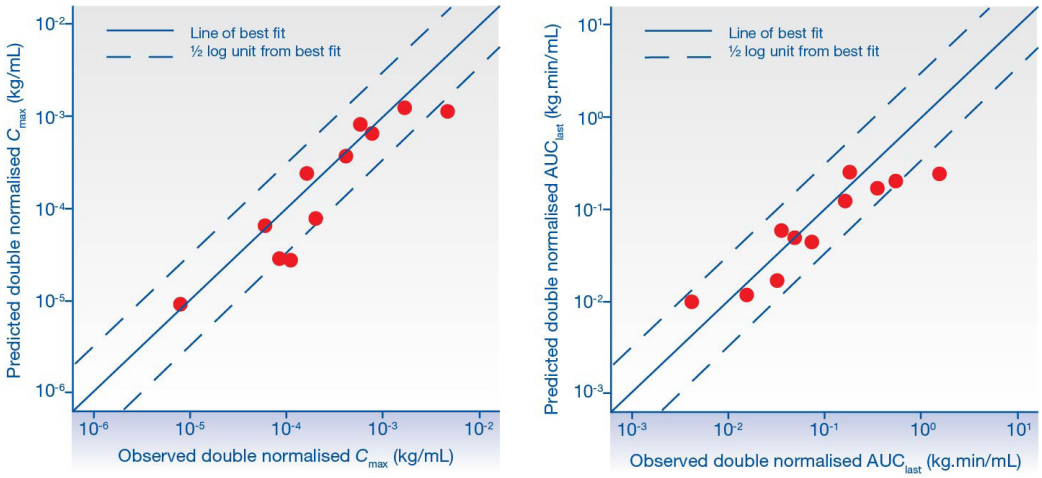


Figure 1

Comparison of predicted and observed C_{max} (left) and AUC (right) for oral dose administration.

Predicted parameters were obtained from Cyprotex's PK prediction service using clearance measured in human hepatocytes. Observed parameters were calculated from clinical plasma profiles. C_{max} and AUC are dose- and body-weight normalised.

The model used in the PK prediction service is a physiologically based PK (PBPK) model[1] and has been trained by optimisation against a set of human *in vivo* plasma profiles. The optimisation process generates datasets from which models for key compound-specific parameters were then developed by machine learning[2] and incorporated into the overall PBPK model framework. This process generates robust and interpretable models that provide, in turn, reliable PK predictions.

Sets of compounds with a diverse range of pharmacokinetic characteristics, distinct from the training set, were selected for testing the model of intravenous and oral PK. The statistics for PK parameter prediction of these compounds are shown below (Table 1).

Parameter	Hepatocytes		Microsomes	
	MFE	Rank	MFE	Rank
Clearance	2.0	0.65	1.8	0.69
Steady state volume of distribution	2.6	0.81	2.7	0.80
Elimination phase volume of distribution	2.5	0.76	2.6	0.72
Half life	2.1	0.60	2.0	0.68
Dose-normalised* C_{max}	1.8	0.94	2.7	0.71
Dose-normalised* AUC	2.0	0.91	3.3	0.54
t_{max}	1.5	0.49	1.3	0.48

Table 1

Statistics for prediction of plasma PK parameters.

MFE = mean-fold error between the predicted and measured PK averaged across all test compounds. *C_{max} and AUC are dose- and body-weight normalised in order to calculate the Spearman's rank correlation coefficient correctly.

Rank = Spearman's rank correlation coefficient between the predicted and measured PK parameter for the test set compounds.

References

[1] Brightman FA *et al.*, (2006) Application of a generic physiologically based pharmacokinetic model to the estimation of xenobiotic levels in human plasma. *Drug Metab Dispos* **34**; 94-101

[2] Krstajic D *et al.*, (2014) Cross-validation pitfalls when selecting and assessing regression and classification models. *J Cheminform* **6**; 10