Application of a PBPK model for prediction of the DDI between Lorazepam and Probencid.
Helen Musther, Silbyle Neuhoff & Karen Rowland Yeo
Simcyp (A Certara Company), Sheffield, UK
helen.musther@certara.com

Background
Drug-drug interactions (DDIs) between lorazepam and probenecid have been observed in vivo with a notable decrease in clearance and increase in AUC (Abemethy et al., 1985). It is suggested this is the result of inhibition of UGT2B7 glucuronidation formation, as there is evidence lorazepam is metabolised mainly by UGT2B7 (Zhang et al., 2007).

Objectives
To apply Physiologically-Based Pharmacokinetic (PBPK) models to assess the UGT2B7-mediated DDI between lorazepam and probenecid in healthy volunteers.

Methods
Lorazepam and Probencid
Physicochemical, in vitro and in vivo information relating to lorazepam and probenecid was obtained from the literature. A full PBPK model was developed for lorazepam within the Simcyp Population-based Simulator (V13 release 2). Reported in vivo CL\textsubscript{iv} and CL\textsubscript{e} were used in combination with in vitro fm data for UGTs to back-calculate a metabolic intrinsic clearance using a retrograde approach. This was then incorporated into the model as UGT2B7 elimination data from a recombinant system. A Kp scalar was applied for the distribution to recover the observed V\textsubscript{ss}.

Simulations were run to generate concentration-time profiles of lorazepam following single (SD) and multiple (MD), intravenous (i.v.) or oral (p.o.) doses over a range of doses (1 mg to 4.5 mg (0.057 mg/kg)) and compared to the available in vivo data.

Simulations of PK profiles of lorazepam and probenecid
The simulated concentration-time profiles of lorazepam were consistent with observed data from 4 independent studies (Figure 2).

Simulations of UGT2B7-mediated DDI
The predicted concentration-time profile, indicating the increase in exposure of lorazepam (2 mg SD) following administration of probenecid was similar to the observed data (Figure 4). The predicted and observed ratios of the area under the plasma concentration-time profile are shown in Table 1. The under-prediction of the DDI may be due to the contribution of additional UGTs (in liver and kidney) that have not been accounted for so far as probenecid is a potent inhibitor towards many UGTs (Uchailchit et al., 2004).

Simulations of PK profiles of lorazepam and probenecid
The simulated concentration-time profiles for probenecid were consistent with observed data for 2 independent studies at the inhibitor dose of 500 mg (Figure 5).

Simulations of UGT2B7-mediated DDI
The predicted concentration-time profile, indicating the increase in exposure of lorazepam (2 mg SD) following administration of probenecid was similar to the observed data (Figure 4). The predicted and observed ratios of the area under the plasma concentration-time profile are shown in Table 1. The under-prediction of the DDI may be due to the contribution of additional UGTs (in liver and kidney) that have not been accounted for so far as probenecid is a potent inhibitor towards many UGTs (Uchailchit et al., 2004).

Conclusions
PBPK modelling in conjunction with reliable inhibition data can be used to assess the importance of interactions affecting the glucuronidation pathways. The reported PBPK models can also be used to evaluate other UGT2B7-mediated DDIs using lorazepam and probenecid as victim and perpetrator, respectively.

References
2. Zhang et al. 2007. DMD 35:2270-2280
4. Rowland et al. 2006. DMD 34:1065-1062
5. Sibby et al. 1996. JCP 28: 240-245

Table 1. Comparisons of observed and predicted AUC values.

<table>
<thead>
<tr>
<th>AUC ratio</th>
<th>Observed</th>
<th>Predicted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>1.83</td>
<td>1.37</td>
</tr>
<tr>
<td>Min</td>
<td>0.97</td>
<td>1.14</td>
</tr>
<tr>
<td>Max</td>
<td>2.82</td>
<td>1.79</td>
</tr>
</tbody>
</table>