Evaluation of the Use of Static and Dynamic Models to Predict Drug-Drug Interaction and Its Associated Variability: Impact on Drug Discovery and Early Development

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ABSTRACT:
Simcyp, a population-based simulator, is widely used for evaluating drug-drug interaction (DDI) risks in healthy and disease populations. We compare the prediction performance of Simcyp with that of mechanistic static models using different types of inhibitor concentrations, with the aim of understanding their strengths/weaknesses and recommending the optimal use of tools in drug discovery/early development. The inclusion of an additional term in static equations to consider the contribution of hepatic first pass to DDIs (AUCIR) has also been examined. A second objective was to assess Simcyp’s estimation of variability associated with DDIs. The data set used for the analysis comprises 19 clinical interactions from 11 proprietary compounds. Except for gut interaction parameters, all other input data were identical for Simcyp and static models. Static equations using an unbound average steady-state systemic inhibitor concentration (Isys) and a fixed fraction of gut extraction and neglecting gut extraction in the case of induction interactions performed better than Simcyp (84% compared with 58% of the interactions predicted within 2-fold). Differences in the prediction outcomes between the static and dynamic models are attributable to differences in first-pass contribution to DDI. The inclusion of AUCIR in static equations leads to systematic overprediction of interaction, suggesting a limited role for hepatic first pass in determining inhibition-based DDIs for our data set. Our analysis supports the use of static models when elimination routes of the victim compound and the role of gut extraction for the victim and/or inhibitor in humans are not well defined. A fixed variability of 40% of predicted mean area under the concentration-time curve ratio is recommended.

Introduction
Drug-drug interactions (DDIs) have an impact on the exposure of a substrate (victim) drug via inhibition/induction of its metabolic pathways by a coadministered inhibitor/inducer (perpetrating) drug. Regulatory guidelines (European Medicines Agency, 2010; http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/05/WC500090112.pdf; U.S. Food and Drug Administration, www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf) recommend that initial DDI risk assessments should be done using in vitro data, because they have been shown to predict interaction within 2-fold of that observed for reversible P450 inhibition-based (Brown et al., 2005; Ito et al., 2005; Obach et al., 2006), time-dependent inhibition-based (Kanamitsu et al., 2000a; Mayhew et al., 2000; Yamano et al., 2001), and induction-based (Ripp et al., 2006; Shou et al., 2008) DDIs. Improved DDI predictions are possible by incorporating in vitro data into mechanistic static or physiologically based models.

AUC ratios have traditionally been estimated with static equations. The prediction accuracy of these models relies on use of an appropriate surrogate for the inhibitor concentration at the active site of the enzyme. Although the use of an unbound inhibitor concentration is considered to be most relevant (Einolf, 2007), the U.S. Food and Drug Administration recommends use of total inhibitor concentration to avoid false-negative results. Average steady-state systemic concentration (Isys), maximum steady-state systemic concentration (Imax), and hepatic inlet concentration (Ihfp) have all been evaluated for use (Ito

ABBREVIATIONS: DDI, drug-drug interaction; P450, cytochrome P450; AUC, area under the concentration-time curve; PK, pharmacokinetic; AZ, AstraZeneca; MDCK, Madin-Darby canine kidney; TDI, time-dependent inhibition; CI, confidence interval; RMSE, root mean square error; GM, geometric mean.
et al., 2004) in static models. For an orally administered inhibitor, $I_{\text{inlet}}$ is an appropriate measure of drug exposure to enzyme during the absorption phase of the inhibitor in the absence of transporter involvement. However, because the absorption phase is short compared with the dosing interval for a once-daily drug, the use of $I_{\text{inlet}}$ may lead to overestimation of DDI risk, especially for a short half-life inhibitor. The use of $I_{\text{sys}}$ on the other hand, could underestimate DDI risk (Ito et al., 2004) because it neglects the higher-than-systemic inhibitor concentration associated with hepatic first pass, especially for high-clearance substrates.

In recent years, Simcyp (Simcyp Limited, Sheffield UK; http://www.simcyp.com), a dynamic, population-based model has been used to predict DDI risk over the entire PK profile of a substrate with dynamically varying inhibitor concentrations. Simcyp enables inclusion of inhibitory metabolites, simultaneous mechanisms of interaction (e.g., inhibition and induction), dose staggering, multiple inhibitors, and inhibition of multiple enzymes. By incorporating sources of variability (enzyme/transporter polymorphism, demography, and differences in ethnicities/disease states), Simcyp aids the design of DDI studies and helps identify individuals who are at extreme risk of DDIs (Cubitt et al., 2011) in a population defined in its database. However, confidence in DDI and variability estimates can be confounded by the large uncertainties associated with the input data in early stages (Fig. 1). Prediction performance of static and dynamic approaches depends on the quality of in vitro data and on the certainty in understanding elimination/metabolic routes and gut extraction for a substrate. Failure to understand the role of transporters or to identify the existence of inhibitory metabolites, concurrent inhibition/induction, compensatory elimination mechanisms, or active metabolites that are potential victims of DDIs can confound predictions. In the preclinical stage, uncertainties in the predicted clearance of victim/inhibitor and/or predicted inhibitor dose can further limit prediction accuracy. In addition, non-P450, renal, and biliary routes identified for the victim in preclinical species may be irrelevant to humans.

A comparison of dynamic and static models covering a wide range of inhibitors, substrates, and enzymes (Einolf, 2007) was disadvantaged by the use of inconsistent input parameters in the two models. A combined static model was compared with Simcyp for 30 DDIs involving midazolam and various CYP3A4 inhibitors (Fahmi et al., 2009). Wang (2010) compared the models for 54 interactions perpetuated by mechanism-based inhibitors of CYP3A4. Guest et al. (2011) used 35 DDIs to compare Simcyp V8’s time-based model with its implementation of static models. All evaluations showed a comparable performance for the two models. Our objective was to use a diverse proprietary data set of 19 DDIs to compare the mechanistic static equations with Simcyp V11, ensuring consistent preclinical input parameters in the models, to understand the reasons for any differences in performance. To avoid the impact that the quality of PK predictions can have on the performance of the tools, clinically observed clearance and distribution parameters have been used for all the 11 AZ compounds. We have not tried to fit a dynamic model to the observed plasma data, as we position our evaluation at the end of the preclinical phase. We also examine the use of an additional term in static equations to consider the contribution from hepatic first pass to DDI. Together with an assessment of Simcyp’s estimates of variability, we suggest an optimal use of DDI prediction tools in drug discovery/early development.

**Materials and Methods**

**Compounds Used in the Study.** The 11 proprietary compounds chosen for this retrospective analysis were either victims or perpetrators of reversible or time-dependent inhibition or induction of CYP3A4 or inhibition of CYP2D6. Clinical interaction studies that involved the inhibition of drug transporters were not included. The compounds selected are from seven disease areas, and their chemical space encompasses a medium to high molecular weight (350–592), loga-

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**Fig. 1.** Sources of uncertainty associated with DDI evaluation in discovery and preclinical phases. CYP, cytochrome P450; rCYP, recombinant cytochrome P450.
Table 1: Overview of the clinical trial design for the 19 drug interaction studies

<table>
<thead>
<tr>
<th>Category of AZ Compounds</th>
<th>Interacting Drug</th>
<th>Victim Drug</th>
<th>Fed/Fasted</th>
<th>n</th>
<th>Age Range</th>
<th>Proportion of Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perpetrators of P450 inhibition</td>
<td>Midazolam</td>
<td>10 12 days, q.d.</td>
<td>7.5</td>
<td>Single, day 5</td>
<td>Fasted</td>
<td>28</td>
</tr>
<tr>
<td>AZ1</td>
<td>Simvastatin</td>
<td>400 5 days, q.d.</td>
<td>0</td>
<td>Single, day 5</td>
<td>Fasted</td>
<td>10</td>
</tr>
<tr>
<td>AZ2</td>
<td>Midazolam</td>
<td>400 5 days, q.d.</td>
<td>0</td>
<td>Single, day 5</td>
<td>Fasted</td>
<td>30</td>
</tr>
<tr>
<td>AZ3</td>
<td>Metoprolol</td>
<td>125 11 days, q.d.</td>
<td>7.5</td>
<td>Single, day 11</td>
<td>Fasted</td>
<td>12</td>
</tr>
<tr>
<td>AZ4</td>
<td>Metoprolol</td>
<td>750 6 days, bid</td>
<td>100</td>
<td>Single, day 6</td>
<td>Fasted</td>
<td>14</td>
</tr>
<tr>
<td>AZ5</td>
<td>Metoprolol</td>
<td>500 28 days, q.d.</td>
<td>50</td>
<td>Single, day 15</td>
<td>Fasted</td>
<td>18</td>
</tr>
</tbody>
</table>

Victims of P450 inhibition

| AZ6 | Ketonezole | 400 5 days, q.d. | 125 | Single, day 3 | Fasted | 22 | 18–65 |
| AZ7 | Verapamil | 240 7 days, q.d. | 0 | Single, day 5 | Fasted | 23 | 18–65 |
| AZ7 | Ketonezole | 200 10 days, bid | 90 | Single, day 4 | Fasted | 14 | 20–45 |
| AZ8 | Diltiazem | 240 14 days, q.d. | 90 | Single, day 8 | Fasted | 17 | 20–45 |
| AZ8 | Ketonezole | 200 4 days, q.d. | 3 | Single, day 4 | Fed | 4 | 22–40 |
| AZ8 | Ketonezole | 100 4 days, bid | 3 | Single, day 4 | Fed | 8 | 20–40 |
| AZ9 | Intraconazole | 200 7 days, q.d. | 10 | Single, day 4 | Fasted | 6 | 30–49 |
| AZ10 | Ketonezole | 200 4 days, q.d. | 25 | Single, day 4 | Fasted | 12 | 24–42 |

Perpetrators or victims of P450 induction

| AZ5 | Rifampicin | 600 16 days, q.d. | 500 | Single, day 10 | Fasted | 18 | 27–56 |
| AZ7 | Rifampicin | 600 12 days, q.d. | 180 | Single, day 12 | Fasted | 16 | 22–49 |
| AZ9 | Rifampicin | 600 13 days, q.d. | 15 | Single, day 10 | Fasted | 12 | 20–61 |
| AZ10 | Carbamazepine | 600 25 days, q.d. | 300 | 35 days b.i.d. | Fed | 18 | 29–63 |
| AZ11 | Midazolam | 10 12 days, q.d. | 5 | Single, day 12 | Fed | 24 | 20–49 |

Determination of In Vitro Interaction Parameters. In-house methods for the in vitro evaluation of cytochrome P450 reaction phenotyping and competitive and time-dependent inhibition as well as induction have been described previously (Zhou et al., 2011). The panel of recombinant P450s in P450 recombinant P450s are listed in Tables 2 and 3, respectively. For AZ4, the measured Ki is $>35 \mu M$. In this case, estimation of DDIs was performed using 35 \mu M.

Simulation of clinical DDI data before initiation of the studies. Studies have been performed in accordance with the Declaration of Helsinki. Informed consent was obtained from all individuals participating in the studies before initiation of the studies.

<table>
<thead>
<tr>
<th>Victim Drug</th>
<th>Impact Factor</th>
<th>Impact Factor (Static Model)</th>
<th>Linear Dose Range from Clinical Phase I Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZ5</td>
<td>1</td>
<td>1</td>
<td>0.5</td>
</tr>
<tr>
<td>AZ6</td>
<td>0.87</td>
<td>1</td>
<td>0.56</td>
</tr>
<tr>
<td>AZ7</td>
<td>1</td>
<td>1</td>
<td>0.43</td>
</tr>
<tr>
<td>AZ8</td>
<td>0.43</td>
<td>1</td>
<td>0.3</td>
</tr>
<tr>
<td>AZ9</td>
<td>0.5</td>
<td>0.16</td>
<td>0.5</td>
</tr>
<tr>
<td>AZ10</td>
<td>0.6</td>
<td>&gt;0.7</td>
<td>0.5</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.94</td>
<td>1</td>
<td>0.57</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>0.93</td>
<td>0.99</td>
<td>0.66</td>
</tr>
</tbody>
</table>
distribution ($V_{ss}$) derived from a single ascending dose or other phase I studies were used. Renal and metabolic clearances used as inputs in Simcyp were also obtained from clinical studies. All physicochemical data and PK parameters that were used in the evaluation are presented in Table 4. Because the clearance of a victim drug will influence the extent of interaction during hepatic first pass, Simcyp’s retrograde calculator was used to compute $CL_{int}$, the total hepatic clearance, from micromolar constant per minute per micromole of enzyme using the clinically observed metabolic clearance as well as the percentage contribution from each of the P450s that were used in the evaluation are presented in Table 4. Because the clearance

\[ CL_{int} = \frac{k_{e}}{k_{m,CYP}} \]

where $k_{e}$ is the enzyme kinetic constant and $k_{m,CYP}$ is the Michaelis constant for the CYP enzyme.

**DDI Predictions with Static Equations.** AUC ratio estimates from the mechanistic static equations in this section differ from static estimates from Simcyp, which are specifically referred to as $R_{exp}$. Henceforth, any reference to AUC ratios from static equations refers only to results from using the equations in this section. The following static equations were used in the prediction of AUC ratios for reversible inhibition, time-dependent inhibition (TDI) (Obach, 2009), and enzyme induction (Almond et al., 2009).

Reversible inhibition (eq. 1):

\[ \frac{AUC_{i}}{AUC} = \frac{f_{gas}}{f_{gas}} \times \frac{\sum_{m} f_{m} \times f_{m,CYP}}{1 + \sum_{m} f_{m} \times f_{m,CYP}} + (1 - \sum_{m} f_{m} \times f_{m,CYP}) \]

where $f_{gas}$ is the fraction of drug unbound, $f_{gas}$ is the fraction of drug unbound in the gut, $f_{gas}$ is the fraction of drug unbound in microsomal incubation, and $f_{gas}$ is the fraction of drug unbound in the gut.

**TABLE 4**

<table>
<thead>
<tr>
<th>Compound input parameters for dynamic and static modeling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Wi.</td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>AZ1</td>
</tr>
<tr>
<td>AZ2</td>
</tr>
<tr>
<td>AZ3</td>
</tr>
<tr>
<td>AZ4</td>
</tr>
<tr>
<td>AZ5</td>
</tr>
<tr>
<td>AZ6</td>
</tr>
<tr>
<td>AZ7</td>
</tr>
<tr>
<td>AZ8</td>
</tr>
<tr>
<td>AZ9</td>
</tr>
<tr>
<td>AZ10</td>
</tr>
<tr>
<td>AZ11</td>
</tr>
</tbody>
</table>

*Note: $V_{ss}$ is the volume of distribution at steady state, $f_{gas}$ is the fraction of absorbed drug escaping gut metabolism, Caco-2/MDCK $P_app$ is the apparent permeability from Caco-2 or MDCK cell lines, $V_{ss}$ is the steady-state volume of distribution, and $CL_{int}$ is the total hepatic clearance.

**TABLE 3**

Inhibitor-related pharmacokinetic and interaction parameters

<table>
<thead>
<tr>
<th>Perpetrator Drug</th>
<th>Type of Inhibition</th>
<th>Affected Enzyme</th>
<th>$f_{gas}$</th>
<th>$k_{a}$</th>
<th>$k_{m}$</th>
<th>$f_{aunc}$</th>
<th>Other Parameters*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AZ1</td>
<td>TDI</td>
<td>CYP3A4</td>
<td>0.88</td>
<td>0.053</td>
<td>0.72</td>
<td>0.00119</td>
<td>$K_{i}$ 9.4; $k_{max}$ 0.056</td>
</tr>
<tr>
<td>AZ2</td>
<td>Competitive inhibitor</td>
<td>CYP3A4</td>
<td>1</td>
<td>0.033</td>
<td>0.5</td>
<td>0.00002</td>
<td>571 $K_{i}$ 3.86</td>
</tr>
<tr>
<td>AZ3</td>
<td>TDI</td>
<td>CYP3A4</td>
<td>1</td>
<td>0.033</td>
<td>0.5</td>
<td>0.00064</td>
<td>18 $K_{i}$ 11.1; $k_{max}$ 0.051</td>
</tr>
<tr>
<td>AZ4</td>
<td>Competitive inhibitor</td>
<td>CYP2D6</td>
<td>0.64</td>
<td>0.005</td>
<td>0.52</td>
<td>0.00289</td>
<td>4 $K_{i}$ 7.9</td>
</tr>
<tr>
<td>AZ5</td>
<td>Competitive inhibitor</td>
<td>CYP2D6</td>
<td>0.88</td>
<td>0.013</td>
<td>1</td>
<td>0.0003</td>
<td>38.6 $K_{i}$ 3.79</td>
</tr>
<tr>
<td>AZ11</td>
<td>Inducer</td>
<td>CYP3A4</td>
<td>0.87</td>
<td>0.033</td>
<td>0.5</td>
<td>0.00134</td>
<td>8.6 28 $E_{max}$; EC_{50} 1.3</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>Competitive inhibitor</td>
<td>CYP3A4</td>
<td>1</td>
<td>0.032</td>
<td>0.5</td>
<td>0.00154</td>
<td>7.5 0.97 $K_{i}$ 0.015</td>
</tr>
<tr>
<td>Verapamil</td>
<td>TDI</td>
<td>CYP3A4</td>
<td>1</td>
<td>0.020</td>
<td>0.6</td>
<td>0.00136</td>
<td>8.5 1 $K_{i}$ 2.21; $k_{max}$ 0.033</td>
</tr>
<tr>
<td>Dilazepm</td>
<td>Inducer</td>
<td>CYP3A4</td>
<td>0.100</td>
<td>0.8</td>
<td>0.00289</td>
<td>4 $K_{i}$ 4.75; $k_{max}$ 0.012</td>
<td></td>
</tr>
<tr>
<td>Tracoxolazone</td>
<td>Competitive inhibitor</td>
<td>CYP3A4</td>
<td>1</td>
<td>0.010</td>
<td>0.7</td>
<td>0.00023</td>
<td>50 0.0013 $K_{i}$ 0.0013</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Inducer</td>
<td>CYP3A4</td>
<td>0.89</td>
<td>0.009</td>
<td>0.5</td>
<td>0.00385</td>
<td>3 $Ind_{max}$ 0.013</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Inducer</td>
<td>CYP3A4</td>
<td>0.84</td>
<td>0.008</td>
<td>0.96</td>
<td>0.00031</td>
<td>37.5 $Ind_{slope}$ 0.16</td>
</tr>
</tbody>
</table>

$f_{gas}$ fraction absorbed; $k_{a}$, absorption rate constant; $f_{gas}$, fraction escaping gut metabolism, assumed to be 0.5 for AZ2, AZ3, ketoconazole, and rifampicin; $k_{i}$, elimination rate constant; $f_{aunc}$, fraction of drug unbound in microsomal incubation; $K_{i}$, reversible inhibition constant; $k_{max}$, maximal enzyme inactivation rate constant measured for a time-dependent inhibitor; $K_{i}$, unbound inhibitor concentration at $50\%$ $k_{max}$; $E_{max}$, fold increase in response over vehicle; $EC_{50}$, inhibitor concentration at $50\%$ $Ind_{max}$; $Ind_{slope}$, calibrated slope of the fold induction versus concentration plot in the linear range of concentrations.

*Units of measure: $K_{i}$, micromolar concentration; $k_{max}$, minute $^{-1}$; $E_{max}$, fold; $EC_{50}$, micromolar concentration; $Ind_{max}$, fold; $Ind_{slope}$, micromolar concentration; $Ind_{slope}$, 1/micromolar concentration.
linearity was ensured (Table 2) in deriving interaction in the gut can be extensive, a good estimate of $f_{gut}$, the fraction of gut metabolism mediated by the induced enzyme and is taken as 1 for compounds in this study, because the only known gut enzyme mediating gut metabolism for the victim compounds is CYP3A4. The inhibitor concentration in the small intestine, $I_{in}$, is calculated using eq. 6c (Obach et al., 2007). $N$ is the number of oral doses per day. $k_u$ is the first-order absorption rate constant, $f_{abs}$ is the fraction of dose absorbed, and $Q_{int}$ is the blood flow rate to the villi and is adopted from Simcyp V11 (6% of cardiac output) for consistency. The fraction of CYP3A4-mediated intestinal metabolism was assumed to be 0.57 and 0.66 for midazolam and simvastatin, respectively, as reported previously (Obach et al., 2007).

Proposed Multiplier to Account for Contribution to AUC Ratio from Hepatic First Pass. For an orally administered inhibitor, the concentration at the enterocytes during its absorption phase is likely to be much higher than its concentration in the liver during hepatic first pass, which in turn is likely to be higher than its systemic concentration at steady state. Equations 1 and 5 account for contributions to DDI from gut and after steady state is attained, but ignore the contribution to DDI from hepatic first pass, if $I_{sys}$ is used. To mitigate the risk for underestimation of DDI due to the neglect of the hepatic first-pass effect for orally coadministered inhibitor and victim, an additional multiplier term that accounts for the contribution to DDI from hepatic first pass ($AUC_{r,hep}$) was introduced into eqs. 1 and 5, such that the overall AUC ratio is a product of contributions to AUC ratio from gut ($AUC_{r,gut}$), hepatic first-pass, and systemic ($AUC_{r,sys}$) inhibition of the affected enzyme. Thus,

$$AUC_{r} = AUC_{r,gut} \times AUC_{r,hep} \times AUC_{r,sys}$$

The contribution to DDI during hepatic first pass of an orally administered inhibitor, $AUC_{r,hep}$, can be given by eq. 7, similar to gut contribution during intestinal first pass:

$$AUC_{r,hep} = \frac{f_{gut}}{f_{int}} - \frac{1 - CL_{substrate}/Q_{int}}{1 - CL_{substrate}/Q_{int}}$$

where $f_{gut}$ and $f_{int}$ are the fractions of the victim drug escaping hepatic first-pass metabolism in the absence and presence of inhibitor, respectively. $Q_{int}$ is the hepatic blood flow rate and $CL_{substrate}$ is the plasma clearance of the substrate compound in the absence of the inhibitor, estimated from clinical PK data as described before. In the absence of intravenous PK, $CL_{substrate}$ is obtained from the best estimate of bioavailability and $CL_{p.o.}$ or $CL_{p.o.}\text{substrate}$ is the plasma clearance of the substrate when coadministered with an inhibitor given by eqs. 8 and 9 for the reversible and time-dependent inhibition, respectively.

$$CL_{substrate} = CL_{substrate} \times \frac{\sum_{n} f_{n,sys} + (1 - \sum_{n} f_{n,sys})}{1 + \sum_{n} k_{inact} \times (k_{u,inlet} + I_n)}$$

and

$$I_n = \frac{Dose 	imes k_u 	imes f_{abs}}{Q_{int} \times N}$$

The mechanistic, static models (eqs. 1, 5, and 6a and incorporating eq. 7 into eqs. 1 and 5) were all compiled in a spreadsheet to enable easy calculation of AUC ratios. Using this spreadsheet, AUC ratios can be calculated for different types of inhibitor concentrations ($L_{sys}$, $L_{max}$, and $L_{inact}$).

**Data Analysis.** The 90% confidence interval (CI) was chosen as measure of variability because it was the statistical parameter used to describe the clinical data. For both AUC and maximum concentration ($C_{max}$) ratios 90% confidence intervals were computed using the output data generated in Simcyp. If $N$ is the size of the population, df, the number of degrees of freedom, is $N - 1$. The upper and lower limits of confidence interval are then given by eq. 10:

$$\ln(CI) = \ln(\text{mean}(AUC\text{ ratio})) \pm \frac{\text{SD}(\ln(AUC\text{ ratio}))}{\sqrt{N}}$$
where \( t_{df} \) is the \( t \) distribution corresponding to \( df \) and \( S \) and \( D \) is the standard deviation. A similar equation was used to describe confidence intervals for the \( C_{\text{max}} \) ratio.

Prediction performance of Simcyp (time-based and \( R_{\text{ss}} \)) as well as that of static equations outlined in this section was judged by the percentage of compounds that were predicted within 2-fold of the observed clinical interaction parameters. When predictions indicate no DDI, contrary to clinical observation, it is considered to be an underprediction, even if the observed AUC ratio (12)

\[
\text{RMSE} = \sqrt{\frac{\sum (\text{predicted DDI} - \text{observed DDI})^2}{\text{Number of predictions} (n)}} \tag{11}
\]

To assess Simcyp’s estimate of variability associated with DDI predictions, the ratio of variance (square of SD) of estimated to clinically observed was calculated (eq. 12):

\[
\text{Variance ratio (Simcyp:observed)} = \frac{\text{Variance of estimated AUC (or } C_{\text{max}})\text{ ratio}}{\text{Variance of clinically-observed AUC (or } C_{\text{max}})\text{ ratio}} \tag{12}
\]

A plot of variance ratio versus GM (Simcyp, observed) should reveal any systematic dependencies of estimated variability on DDI magnitude.

### Results

The 19 DDI clinical trials from the 11 AstraZeneca compounds were subdivided into three categories:

A. AstraZeneca compounds that are perpetrators of reversible or irreversible P450 inhibition

B. AstraZeneca compounds that are victims of reversible or irreversible P450 inhibition

C. AstraZeneca compounds that are victims or perpetrators of P450 induction

Table 5 summarizes the clinically observed interaction parameters as well as predicted values using Simcyp and mechanistic static equations for all the 19 interactions falling into the three categories. Table 6 lists the RMSEs for all static and dynamic predictions of DDI. The use of unbound \( I_{\text{sys}} \) in static equations (eqs. 1 and 5) is

| TABLE 5 |

Summary of observed and predicted (Simcyp V11 and static equations with \( I_{\text{sys}} \)) DDI

<table>
<thead>
<tr>
<th>Interactions involving category A AZ compounds</th>
<th>Observed</th>
<th>Simcyp V11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interactions involving category B AZ compounds</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interactions involving category C AZ compounds</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| TABLE 6 |

RMSE for static and dynamic DDI predictions

<table>
<thead>
<tr>
<th>RMSE</th>
<th>Simcyp AUC ratio</th>
<th>( R_{\text{ss}} ) Time-based</th>
<th>Simcyp ( C_{\text{max}} ) ratio: time-based</th>
<th>Static AUC ratio: ( I_{\text{sys}} ) without first pass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.7</td>
<td>12.9</td>
<td>5.9</td>
<td>4.7</td>
</tr>
<tr>
<td></td>
<td>43.7</td>
<td>12.9</td>
<td>5.9</td>
<td>14.9</td>
</tr>
<tr>
<td></td>
<td>43.7</td>
<td>12.9</td>
<td>5.9</td>
<td>2.4</td>
</tr>
</tbody>
</table>

\( R_{\text{ss}} \) AUC ratio from Simcyp V11 using the default average systemic inhibitor concentration at steady state; N.A., not available; GM, geometric mean.

\( a \) First pass refers to hepatic first-pass contributions for the P450 inhibition interactions and intestinal gut contributions for P450 induction interactions (the last five interactions).

### Table 5

<table>
<thead>
<tr>
<th>Interactions involving category A AZ compounds</th>
<th>Observed</th>
<th>Simcyp V11</th>
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</thead>
<tbody>
<tr>
<td>Interactions involving category B AZ compounds</td>
<td></td>
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<tr>
<td>Interactions involving category C AZ compounds</td>
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</tbody>
</table>

| TABLE 6 |

RMSE for static and dynamic DDI predictions

<table>
<thead>
<tr>
<th>RMSE</th>
<th>Simcyp AUC ratio</th>
<th>( R_{\text{ss}} ) Time-based</th>
<th>Simcyp ( C_{\text{max}} ) ratio: time-based</th>
<th>Static AUC ratio: ( I_{\text{sys}} ) without first pass</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>43.7</td>
<td>12.9</td>
<td>5.9</td>
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<tr>
<td></td>
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</tr>
</tbody>
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\( R_{\text{ss}} \) AUC ratio from Simcyp V11 using the default average systemic inhibitor concentration at steady state; N.A., not available; GM, geometric mean.

\( a \) First pass refers to hepatic first-pass contributions for the P450 inhibition interactions and intestinal gut contributions for P450 induction interactions (the last five interactions).
associated with the lowest RMSE. This finding is also evident from Fig. 2, which shows a comparison of AUC ratios from static equations using the three different types of inhibitor concentrations: \( I_{sys} \), \( I_{inlet} \), and \( I_{max} \) for the inhibition-based interactions. \( I_{inlet} \) and \( I_{max} \) tend to overpredict the interaction risk. Therefore, \( I_{sys} \) was used in all evaluations with the static equations for comparison with the time-based Simcyp predictions. With the inclusion of hepatic first-pass correction (eq. 7) into mechanistic static eqs. 1 and 5, systemic inhibition with \( I_{sys} \), hepatic first-pass inhibition with \( I_{inlet} \), and gut enzyme inhibition with the \( f_{gut} \) would be considered. However, inclusion of AUCR_{hfp} tends to overpredict the DDI risk. The overall accuracy decreased (see RMSE in Table 6).

Clinically observed interactions for the 11 compounds were moderate (AUC ratio ≤5) for category A compounds and moderate to strong (strong being AUC ratio >5 for inhibition and <0.2 for induction) for the category B and C compounds. No clinical AUC

![Fig. 2. Mechanistic static equation predictions of AUC ratios versus clinically observed for P450-based drug interactions in category A and category B compounds. Line of unity and 2-fold limits are indicated.](image)

\( I_{sys} \), \( I_{inlet} \), and \( I_{max} \) are the average systemic steady-state, hepatic inlet, and maximum systemic steady-state inhibitor concentrations, respectively.

![Fig. 3. Simcyp time-based AUC ratios and \( R_{ss} \) predictions versus clinically observed for 19 drug interactions. Line of unity and 2-fold limits are indicated.](image)
ratios were >10-fold. This is also evident in Fig. 3, in which time-based AUC ratios and $R_{ss}$ from Simcyp are plotted against the clinically observed AUC ratios for all three categories of compounds. Whereas the clinical AUC ratios of the interactions studied range between 0.1 and 10, Simcyp-predicted ratios (both time-based and $R_{ss}$) exceed this range, especially for larger AUC ratios. Because the hepatic outlet (or systemic) inhibitor concentration was used in the estimation of $R_{ss}$, it should be comparable to results from static models with unbound $I_{sys}$, presented in the last column of Table 5. However, $R_{ss}$ consistently overpredicts DDIs compared with AUC ratios from eqs. 1 to 3, possibly because of differences in the estimation of gut contributions to DDIs. This is especially true for CYP3A4-mediated interactions. Therefore, only time-based predictions from Simcyp have been used for the comparative analysis with static equations. Figure 4 shows the predicted and observed AUC ratios for the three categories of compounds. Prediction performance of Simcyp V11 and that of the best of the static equations ($I_{sys}$ with and without hepatic first-pass correction) are shown in Table 7.

Among the 19 interactions studied, the AZ5-metoprolol interaction is the only non-CYP3A4 interaction for which the predicted AUC ratio is >1 and for which the AUC ratios from both Simcyp and mechanistic static models match. Because the gut contribution to DDI is irrelevant for CYP2D6-mediated interactions, the static and Simcyp predictions for these interactions can be expected to be similar, suggesting that differences in $f_{gut}$ between the two methods may be the reason for differences in their prediction of AUC ratios. A comparison of $f_{gut}$ used in static equations with those estimated in Simcyp for the eight victim compounds in this study show no correlation between the two (Fig. 5). If $f_{gut}$ predicted by Simcyp is low, as in the case of simvastatin and AZ7 (Table 2), then DDIs mediated by the inhibition of gut enzymes will be overpredicted by Simcyp, leading to a large AUC ratio.

For category A, two of the six interactions are mediated by CYP2D6 and the remaining by CYP3A4. The overprediction of the AZ1-simvastatin interaction by Simcyp is probably due to the low gut bioavailability (0.09) predicted by Simcyp for the victim compound.

![Figure 4](image-url)
simvastatin, as explained above. For the AZ4-metoprolol interaction, both Simcyp and static models predict no AUC change, whereas a less than 2-fold AUC change is observed clinically. Obviously, in this case, the measured in vitro $K_i$ did not capture the observed interaction, which is probably mediated by TDI or by an inhibitory metabolite in vivo. This interaction has been included in the analysis only to illustrate that a negative in vitro result need not necessarily hold in vivo. AZ5 being lipophilic, the predicted $f_{uu,mic}$ very low. Any error in this prediction could lead to substantial changes in the estimated AUC ratio. A sensitivity analysis was therefore performed (Supplemental Fig. 1). The AUC ratio goes from approximately 1.3 to 1 in the full range of $f_{uu,mic}$. In the case of AZ5, an imprecise prediction of $f_{uu,mic}$ had little effect on the overall result.

For category B, AZ compounds were victims of CYP3A4 inhibition. The product $f_{m,m,CYP}$ is nearly 1 for all except for AZ9. The AZ6-ketoconazole interaction is the only one for which the ketoconazole dose was 400 mg. Ketoconazole exhibits dose-dependent PK (Huang et al., 1986), possibly due to autoinhibition. A lower oral clearance of 7.4 l/h (Huang et al., 1986) at 400 mg was used both in Simcyp and in static equations. The AUC ratio predicted by static equations improves slightly from 6.4 to 8.1 with the use of lower hepatic clearance. The interaction of AZ7 with ketoconazole is overpredicted by Simcyp. $f_{uu}$ estimated by Simcyp was 0.08 compared with 0.43 (see Table 2) used in static equations. AZ7 is a highly bound ($f_{up} > 0.99$) compound, and, in this case, fixing $f_{uu,p}$ may be invalid. The sensitivity of $f_{uu}$, CL_{p.o.}, and mean AUC ratio to $f_{uu}$ for the AZ7-ketoconazole interaction is presented in Supplemental Fig. 2. Fixing $f_{uu}$ closer to the $f_{up}$ of AZ7 gave a more accurate AUC ratio of 4 for the AZ7-ketoconazole interaction (communications with staff at Simcyp Ltd). For the AZ7-diltiazem interaction, the additional contribution to CYP3A4 inhibition from the metabolite of diltiazem (Rowland Yeo et al., 2010) is built into Simcyp. Likewise, for the AZ9-itraconazole interaction, inhibition by the metabolite of itraconazole is considered in Simcyp. These were not considered in static equations. AZ9 is not a very sensitive substrate because it has a low $f_{m,m,CYP}$ and low clearance. Thus, although the metabolites are known to be more potent in vitro than the parent and account for ~50% of the overall CYP3A inhibition in vivo (Templeton et al.,

<table>
<thead>
<tr>
<th>$f_{uu}$ Simcyp V11 (Time-Based)</th>
<th>Static Equations</th>
<th>$f_{uu}$ Simcyp V11 (Time-Based)</th>
<th>Static Equations</th>
<th>$f_{uu}$ Simcyp V11 (Time-Based)</th>
<th>Static Equations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without Hepatic First-Pass Correction</td>
<td>With Hepatic First-Pass Correction</td>
<td>Without Hepatic First-Pass Correction</td>
<td>With Hepatic First-Pass Correction</td>
<td>Without Hepatic First-Pass Correction</td>
<td>With Hepatic First-Pass Correction</td>
</tr>
<tr>
<td>A 6 3 5 3</td>
<td>2 0 2</td>
<td>1 1 1</td>
<td>C 5 4 4 N.C.</td>
<td>1 1 1</td>
<td>N.C.</td>
</tr>
<tr>
<td>B 8 4 7 6</td>
<td>1 1 2</td>
<td>3 0 0</td>
<td>N.C.</td>
<td>1 1 1</td>
<td>N.C.</td>
</tr>
</tbody>
</table>

N.C., not calculated.

![Fig. 5. Comparison of $f_{uu}$ values used in static models with those generated in Simcyp V11 for victims of P450 inhibition.](image-url)
AUC ratio from 1, the greater is the variance, which is to be expected. Because AZ10 has a very high CLp.o., the difference between the 2 approaches is also large. Unlike Simcyp, the mechanistic static models do not consider interaction during hepatic first pass. The inclusion of AUCRgut in the static DDI estimation should provide a value closer to that from Simcyp. Simcyp reports an estimated systemic clearance of 33 l/h from CLp.o. and f_{gut} (0.5) provided as input, whereas the static equation uses 13.6 l/h, a low value arising from the low bioavailability of AZ10. Therefore, the estimated AUCRgut correction is low (1.12). With use of a clearance value of 33 l/h, the AUCRgut correction is 1.4 and the AUC ratio using the static model becomes 5.6.

It is worthwhile to note that for 15 of the 16 interactions for which C_{\text{max}} ratios were available, the DDI risk indicated by clinical C_{\text{max}} ratios was less than or comparable to (AZ8-ketoconazole interaction) that corresponding to AUC ratios. This finding is in keeping with the smaller range of C_{\text{max}} ratios compared with AUC ratios reported for 54 clinical DDIs involving mechanism-based CYP3A inhibitors (Wang, 2010). Assuming that C_{\text{max}} is affected by first pass, this reflects a reduced importance of first pass (hepatic, intestinal, or both) in DDIs. One explanation could be that whereas the magnitude of the AUC ratio depends only on the extent of intestinal and/or hepatic extraction, the magnitude of the C_{\text{max}} ratio would, in addition to these, depend on the region of the gastrointestinal tract where maximum absorption of substrates occurs. Substrates of an inhibited intestinal enzyme that has high permeability are more likely to have C_{\text{max}} ratios that are comparable to their AUC ratios, if, like CYP3A4, the inhibited enzyme is expressed mainly in the small intestine (Paine et al., 2006). The AZ6-ketoconazole interaction has a relatively large deviation of the C_{\text{max}} ratio from its AUC ratio. If this interaction is compared with the AZ8-ketoconazole interaction, we note that the victim drugs in both interactions have similar clearance. However, the permeability of AZ8 is much higher than that of AZ6, which supports the hypothesis that maximum absorption in the jejunal region where CYP3A4 expression is maximum would result in AZ8 having a C_{\text{max}} ratio comparable to its AUC ratio.

Category C represents induction-mediated interactions. Static equation calculations have been done using \( f_{\text{sys}} \) with and without the gut contributions to DDIs. Inclusion of gut interaction seems to overestimate the risk, especially for interactions with rifampicin. For carbamazepine, Simcyp uses the calibrated slope of the fold induction versus concentration plot in the linear range of concentrations, \( \text{Ind}_{\text{slope}} \). For carbamazepine the value of \( \text{Ind}_{\text{slope}} \) used in Simcyp is 0.16. Static equations used \( E_{\text{max}} \) and EC_{50} values (7.7-fold and 40 \( \mu \)M, respectively) from the literature (McGinnity et al., 2009). It is clear from Table 5 that predictions of AUC ratios from Simcyp and static equations are comparable. Many previous evaluations (Einolf, 2007; Youdim et al., 2008; Fahmi et al., 2009; Perdaens et al., 2010) have shown similar prediction success with Simcyp.

Geometric means, 90% confidence intervals, and variances for the 19 interactions are shown in Table 5. Figure 6, A and B, shows that the variances in the AUC ratio and C_{\text{max}} ratio are not independent of their corresponding geometric means. The greater the deviation of the AUC ratio from 1, the greater is the variance, which is to be expected. This finding is also evident from Fig. 4, in which the absolute extent of variability is seen to be proportional to the mean values of AUC and C_{\text{max}} ratios. Figure 4 also shows that the clinical variability in terms of 90% confidence interval ranges roughly between 10 and 40% of observed AUC ratios, whereas estimated variability covers a broader range. Figure 6C shows the variance ratio (Simcyp, observed) plotted against the GM (Simcyp, observed). This ratio should be 1 for all interactions, if the estimated variability matches the observed. If arbitrary acceptance limits of 2-fold of observed (shown by dotted lines in Fig. 6C) are set, it can be seen that Simcyp tends to over- or underestimate the variability for a considerable number of interactions, depending on the mean values. In addition to this, overprediction of mean AUC ratio by Simcyp, as in the case of the AZ1-simvastatin or AZ7-ketoconazole interaction, can further exaggerate its variability estimation.

Clinical and Simcyp-predicted PK parameters for all AZ compounds are provided in Supplemental Tables 1 and 2.

**Discussion**

Static equations using the unbound average steady-state systemic inhibitor concentration (\( f_{\text{sys}} \)) have been shown to perform better with respect to accuracy than Simcyp V11 for the 19 interactions studied in this report (84 and 58% of the interactions predicted within 2-fold, respectively). Other retrospective validations (Wang, 2010; Guest et al., 2011; Shardlow et al., 2011) indicate comparable predictions. Guest et al. (2011) reported that Simcyp and static models predicted 71 and 77%, respectively, of the DDIs within 2-fold. The authors attributed the comparability to high potency and large dosing of the inhibitors in their study. The higher prediction accuracy of Simcyp reported by Guest et al. (2011) could also have occurred because the validation compounds in their study were all well-characterized azole inhibitors and benzodiazepine substrates.

Differences in the prediction outcomes between static and dynamic models can be attributed to differences in the treatment of hepatic and intestinal first pass and to differences in inhibitor concentration. In addition, the neglect of metabolite inhibition and auto-inactivation of the affected enzyme by a time-dependent inhibitor in static models can lead to an underestimation of DDI risk. AUC ratios from Simcyp exceeding 10-fold should be treated with caution, because clinical interactions rarely exceed that limit (Brown et al., 2005). This study has identified a significant risk for overestimating DDI liability with Simcyp, largely attributable to uncertainty in CYP3A-mediated intestinal DDIs. This result is consistent with a recent report (Sinha et al., 2012). In the gut, CYP3A represents the principal drug-metabolizing P450 enzyme (Paine et al., 1997, 2006). The high gut concentrations of an orally administered inhibitor and the significant intestinal extraction of a substrate despite the low gut CYP3A4 content of just \( \sim 1\% \) of that found in liver (Paine et al., 1997) translate to a significant gut contribution to DDIs. In addition, although CYP3A4 (a low-affinity, high-capacity enzyme)-mediated DDIs could be limited by alternative metabolic/elimination pathways in the liver, intestinal CYP3A4-mediated DDIs could still be high, because CYP3A is almost the only P450 enzyme in the gut. Thus, difficulty in assessing \( f_{\text{gut}} \) of a substrate or inhibitor in Simcyp due to uncertainties in \( f_{\text{sys}} \) and/or due to quality of in vitro data could result in a substantial deviation of predicted DDI from that observed. An underestimation of substrate \( f_{\text{gut}} \) would mean underestimation of DDI risk (due to underestimation of substrate gut metabolism), whereas underestimation of inhibitor \( f_{\text{gut}} \) would mean overestimation of DDI risk (due to higher inhibitor concentration resulting from neglect of gut extraction). Information on human-relevant gut metabolism is sparse in drug discovery. Even during clinical development, such information requires...
an additional intravenous clinical PK study to be done to be able to
distinguish between gut and hepatic first pass. When multiple gut
enzymes (e.g., CYP3A4 and UGT2B7) are involved, an assessment of
the relative contribution to 
\( f_{\text{gut}} \) is an additional challenge. The use of
an estimated \( f_{\text{gut}} \) value in static equations is therefore an attractive
alternative to using the dynamic model for predicting the AUC ratio
of CYP3A-mediated DDI. In the absence of an \( f_{\text{gut}} \) estimate in
humans, an assumption of \( f_{\text{gut}} = 0.5 \) is suggested for CYP3A sub-
strates (S. Peters, unpublished analysis). Because competition with
permeability is likely to limit gut metabolism, compounds with fairly
good permeability cannot have very high extraction in the gut. Thus,
if the extent of gut metabolism is not capacity-limited, a central value
of 0.5 can be rationalized. Interactions involving substrates with large
deviations of \( f_{\text{gut}} \) from those used in static equations were either
under- or overpredicted by Simcyp, which further lends support for an
\( f_{\text{gut}} \) of 0.5.

Hepatic first-pass correction to overcome a possible underprediction
of DDI with the use of \( I_{\text{sys}} \) in static equations, resulted in
systematic overprediction of DDI risk. However, this may be a useful
approach to estimate a maximum expected risk, especially for high-
clearance drugs for which it can make a substantial difference. The
importance of hepatic first pass may depend on the nature of the
interacting compounds. \( C_{\text{max}} \) is seen as critical in summarizing the
DDI risk. However, the clinical interaction data used in this study
show that \( C_{\text{max}} \) ratios are generally less than the AUC ratios. Thus,
AUC ratio prediction should provide an adequate estimate of the
maximum DDI risk.

To further understand the basis for the differences in AUC ratios
predicted by Simcyp (time-based), Simcyp \( R_{\text{sys}} \), and the proposed
static equations, we need to consider the differences in inhibitor
concentrations in the three approaches. Because the aim of clinical
DDI studies is to achieve a steady-state inhibitor concentration, before
administration of the victim, differences in average inhibitor
concentrations and therefore DDI can be expected to be minimal in the three
approaches for inhibitors that are administered intravenously. How-
ever, for orally administered inhibitors that are not metabolized in the
gut, the higher-than-systemic hepatic concentrations during the
absorption phase implies that the use of a single uniform inhibitor
concentration in static equations is likely to under- or overestimate
DDI, depending on whether a systemic or hepatic inlet concentration

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**Fig. 6.** Variance ratios (Simcyp V11: clinic) for AUC (a) and \( C_{\text{max}} \) (b) ratios versus geometric means of the geometric mean values of Simcyp-estimated and clinically observed. c, plot of variance ratio (Simcyp V11: clinic) vs. geometric mean of the geometric means of the Simcyp-estimated and clinically observed interaction ratios. Dotted lines indicate arbitrary limits of acceptable variability (2-fold). Trend lines are also shown.
is used, as in the estimation of $R_{\text{sys}}$. The proposed static equations using $I_{\text{sys}}$ and incorporation of AUC$_{\text{hfp}}$ should be expected to perform better. In the case of time-based Simcyp, the high levels of inhibitor concentrations in the portal vein are valid only during the absorption phase, reflecting the reality. In our analysis, because $I_{\text{sys}}$ has been chosen for $R_{\text{sys}}$ estimation, we should expect Simcyp $R_{\text{sys}}$ and static equations with $I_{\text{sys}}$, to give similar results for non-CYP3A substrates. Finally, for orally administered inhibitors that are metabolized in the gut, high inhibitor concentrations in the gut need to be additionally considered. In the $R_{\text{sys}}$ method, $I_{\text{sys}}$ is a constant high value, explaining its tendency to overpredict the CYP3A-mediated interaction, whereas in the static equations proposed in this study, it is simply dependent on estimated $f_{\text{gut}}$ and on the validity of assuming maximal inhibition of gut enzymes by the inhibitor. In Simcyp (time-based), the dynamically varying inhibitor concentration starts off at a high value but drops substantially over the absorption phase. Thus, differences in the inhibitor concentration ([I]) during hepatic and/or intestinal first pass make the three approaches different. Simcyp’s dynamic treatment of [I] should be expected to provide a better prediction of DDIs under conditions when the inhibitor concentration is not at steady state (e.g., the intended human dose schedule is not long-term). However, uncertainties in the input used in the two models (Fig. 1) can dominate prediction performance and can offset any advantages of a dynamic approach. Simple models with fewer input data are therefore preferable for DDI predictions.

The neglect of autoinhibition and auto-inactivation of the affected enzyme by AZ1 to AZ5 would lead to an underprediction of DDI risk, because it amounts to neglecting the prolonged high concentrations of the inhibitor. Simcyp accounts for the auto-inactivation by the mechanism-based inhibitors, AZ1 and AZ3, but, with the input provided, it cannot consider the autoinhibition by the reversible inhibitors, AZ2, AZ4, and AZ5. Static equations do not consider either of these. Because there is no information on the clinical relevance of autoinhibition, it is difficult to quantify its impact.

With the exception of the AZ10-carbamazepine interaction, all induction interactions were predicted well with static equations, if the gut contribution to DDI is ignored. Inclusion of the gut contribution results in an overestimation of DDI risk. A rationale for this result could be that an increase in gut enzymes due to induction may not really affect the extent of metabolism of the victim compound, because there is a competition between permeability and metabolism in the enterocytes. Therefore, enzyme capacity may have a lesser role than might be anticipated in the absence of a competition from permeability. Victim compounds of induction in this analysis have logP of at least 0.88 and good permeability. Because dynamic models can consider the effect of permeability on the rate and extent of gut metabolism, Simcyp’s estimation of AUC ratios agree with clinically observed values.

This study demonstrated a tendency for Simcyp-estimated variability to be under- or overpredicted, depending on the mean value. Thus, when the mean AUC ratios are themselves overpredicted by Simcyp, the associated variability is likely to be exaggerated for extreme individuals in a population. Because the variability associated with clinical DDI parameters is generally <40% of the mean values, this study recommends a conservative estimate of 40% of predicted mean AUC ratio estimated by mechanistic static equations as a rule of thumb. This recommendation is consistent with the proposed coefficient of variation for CYP3A4 content of 41% (Cubitt et al., 2011) and 33% (Kato et al., 2010). A fixed variability that is slightly higher than the clinically observed margins will have the advantage of covering for any prediction uncertainty and/or higher clinical variability.

In conclusion, this analysis highlights the importance of characterizing the gut and hepatic metabolism of a substrate as well as its major elimination routes in human. This is possible only through having at least the intravenous clinical PK of the substrate. In the absence of relevant information, the use of unbound $I_{\text{sys}}$ in mechanistic static equations with an estimated $f_{\text{gut}}$ in mechanistic static equations with a neglect of gut interactions for induction-mediated DDI can provide reasonable predictions. Considering the possibility for large deviations of Simcyp-predicted AUC ratios from those observed, a fixed measure of variability around the mean static equations-predicted AUC ratios appears to be preferable over a population-based approach during early development phases for assessing the potential for individuals with extreme interactions to experience adverse events. However, during later clinical development, a population-based approach can be valuable in simulating the simultaneous impact of disease, ethnicity, age, and multiple inhibitors (including potent metabolites) as well as enzyme and transporter polymorphism on DDIs.

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Authorship Contributions

Participated in research design: Peters.
Performed data analysis: Peters, Schroeder, and Giri.
Wrote or contributed to the writing of the manuscript: Peters, Schroeder, and Dolgos.

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Drug Metab Dispos 29:443–452.
Curr Drug Metab 8:676–684.
Drug Metab Dispos 39:703–710.

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