Introduction to DDI Simulator

Demonstration of DDI Simulator
Contents

1. Overview of DDI Simulator
   1–1. Main Features
   1–2. Validity of Results
   1–3. Advantages

2. Demonstration
   2–1. Substrate (victim drug)
   2–2. Mechanism-based inhibitor

3. Future Plans
Main Features of DDI Simulator

(1) Quantitative predictions by PBPK model
(2) Database of *in vivo* Ki
(3) Approximation of *in vivo* Ki from *in vitro* Ki
(4) Inhibition of multiple CYP isoforms
(5) Inhibition of intestinal metabolism
(6) Dosing regimen optimization
(7) Batch Simulations
(1) Quantitative Predictions by PBPK model

Physiologically-based Pharmacokinetic (PBPK) Model

**Types of Inhibition**

1. Competitive
   \[ Ki \]
2. Mechanism-based (MBI)
   \[ Ki_{app}, k_{inact} \]

**Advantages of using PBPK model**

- More accurate predictions than simple approximation method
- Allows prediction using in-house compound as inhibitor or substrate
- Evaluate DDI risks based on changes in AUC, Cmax or t1/2

(2) Database of *in vivo* Ki

*in vivo* Ki values were obtained by fitting clinical data.
(3) Approximation of *in vivo* Ki from *in vitro* Ki

*In vivo* Ki values are automatically estimated from *in vitro* Ki using the Ki ratio and clogP relationship shown below.

**Equation:**

\[ y = 4.4525e^{-1.339x} \]

**R²:** 0.8597

**Graph:**

- **Ki ratio vs. clogP**
- **y = 4.4525e^{-1.339x}**
- **R² = 0.8597**
(4) Inhibition of Multiple CYP Isoforms

Only CYP isoforms with fm (fraction of metabolism) values assigned are subject to inhibition.
Maximum inhibitions of intestinal metabolisms are considered only for CYP3A4 substrates by automatically setting FaFg to 1.
Minimize DDI risks by adjusting the substrate dose timing and/or frequency
(7) Batch Simulations

Compare DDI risks of a given compound with several known inhibitors/substrates
1–2 Validity of Results

Objective

Compare simulation results with the values reported from literature

Simplified Method

PBPK Model

Maximum inhibition of intestinal metabolism

○ : CYP3A4 substrates
● : non-CYP3A4 substrates

Objective
Compare simulation results with the values reported from literature

Simplified Method

PBPK Model

Maximum inhibition of intestinal metabolism

○ : CYP3A4 substrates
● : non-CYP3A4 substrates
Inhibitor: Itraconazole \textit{in vitro} \( Ki = 132 \text{ (µg/L)} \), as CYP3A4 competitive inhibitor

Substrate: Triazolam as CYP3A4 substrate

Reported literature:

DDI:

\[ \text{Triazolam(µg/L)} \]

\[ \begin{array}{c}
\text{■ with itraconazole 200mg} \\
\text{▲ with placebo} \\
\end{array} \]

\( C_{\text{maxRatio}} = 3.1 \)


Dosing Regimen:

Itraconazole 200mg repeated 1/day for 4 days

Triazolam 0.25mg administered once on the 4\textsuperscript{th} day
1–2 Validity of Results

Confirm PK parameters in DDI Simulator

<table>
<thead>
<tr>
<th></th>
<th>9 Glimepiride</th>
<th>10 Haloperidol</th>
<th>11 Imipramine</th>
<th>28 Indinavir</th>
<th>29 Itraconazole</th>
<th>30 Ketoconazole</th>
<th>12 Methylprednisolone</th>
<th>13 Metoprolol</th>
<th>14 Midazolam</th>
<th>15 Nifedipine</th>
<th>34 Paroxetine</th>
</tr>
</thead>
<tbody>
<tr>
<td>PK parameters</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
<td>&lt;None&gt;</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>1A2</th>
<th>2C8</th>
<th>2C9</th>
<th>2C19</th>
<th>2D6</th>
<th>3A4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ki&lt;sub&gt;vitro&lt;/sub&gt; [μg/L]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>132</td>
<td></td>
</tr>
<tr>
<td>Ki&lt;sub&gt;vivo&lt;/sub&gt; [μg/L]</td>
<td></td>
<td></td>
<td></td>
<td>0.282</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Itraconazole

in vitro Ki

in vivo Ki

PK parameters in vivo Ki
## 1-2 Validity of Results

### Selecting Drug Pair for Simulation

#### Substrate

<table>
<thead>
<tr>
<th>ID</th>
<th>Substrate Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Diazepam</td>
</tr>
<tr>
<td>8</td>
<td>Fluvastatin</td>
</tr>
<tr>
<td>9</td>
<td>Glimepiride</td>
</tr>
<tr>
<td>10</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>11</td>
<td>Imipramine</td>
</tr>
<tr>
<td>12</td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td>13</td>
<td>Metoprolol</td>
</tr>
<tr>
<td>14</td>
<td>Midazolam</td>
</tr>
<tr>
<td>15</td>
<td>Nifedipine</td>
</tr>
<tr>
<td>34</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>32</td>
<td>Quinidine</td>
</tr>
<tr>
<td>16</td>
<td>Sildenafil</td>
</tr>
<tr>
<td>17</td>
<td>Simvastatin</td>
</tr>
<tr>
<td>18</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>19</td>
<td>Tirilazad</td>
</tr>
<tr>
<td>20</td>
<td>Tolbutamide</td>
</tr>
<tr>
<td>21</td>
<td>Triazolam</td>
</tr>
<tr>
<td>22</td>
<td>Zopiclone</td>
</tr>
</tbody>
</table>

#### Inhibitor

<table>
<thead>
<tr>
<th>ID</th>
<th>Inhibitor Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>24</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>25</td>
<td>Fluconazole</td>
</tr>
<tr>
<td>26</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>27</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>28</td>
<td>Iodinavir</td>
</tr>
<tr>
<td>29</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>30</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>31</td>
<td>Propafenone</td>
</tr>
<tr>
<td>32</td>
<td>Quinidine</td>
</tr>
</tbody>
</table>

- **Triazolam**
- **Itraconazole**
1–2 Validity of Results

Dosing Regimen

**Substrate**

- **Triazolam**
  - Dose [mg]: 0.25
  - No. of times per day: 1

**Inhibitor**

- **Itraconazole**
  - Dose [mg]: 200
  - No. of times per day: 1
  - No. of days: 4

**Substrate Timing**

- Start at: 0 [h] after inhibitor dose number: 4

**Preview**

- **Inhibitor**
  - day 1
  - day 2
  - day 3
  - day 4

- **Substrate**

**Graphs**

- **Substrate**
  - Concentration [µg/l] vs. Time [hours]

- **Inhibitor**
  - Concentration [µg/l] vs. Time [hours]
1-2 Validity of Results

Simulation Results

Ki values used in simulation

- **in vitro Ki**
- **predicted in vivo Ki**
- **predicted in vivo Ki (FaFg=1)**

Maximum inhibition of CYP3A4 in the intestines


- with itraconazole 200mg
- with placebo

CmaxRatio = 3.1
## 1–3 DDI Simulator Advantages

<table>
<thead>
<tr>
<th>Item</th>
<th>Functionality</th>
<th>DDI Simulator</th>
<th>Simplified Method</th>
<th>DDI Simulator Advantages</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prediction</strong></td>
<td><strong>Prediction method used</strong></td>
<td>PBPK</td>
<td>1+I/Ki</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>DDI risk criteria</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>AUC ratio</td>
<td>○</td>
<td>△</td>
<td>Less &quot;false positive&quot; predictions</td>
</tr>
<tr>
<td></td>
<td>Cmax ratio</td>
<td>○</td>
<td>×</td>
<td>Verify risk due to rise in Cmax</td>
</tr>
<tr>
<td></td>
<td>half–life</td>
<td>○</td>
<td>×</td>
<td>Verify risk due to prolonged half–life</td>
</tr>
<tr>
<td></td>
<td>as inhibitor</td>
<td>○</td>
<td>△</td>
<td>Better prediction accuracy</td>
</tr>
<tr>
<td></td>
<td>as substrate</td>
<td>○</td>
<td>×</td>
<td>Verify risk of becoming a victim drug</td>
</tr>
<tr>
<td><strong>DB</strong></td>
<td><strong>PK parameters of well–known substrates/inhibitors (incl. <em>in vivo</em> Ki)</strong></td>
<td>○</td>
<td></td>
<td>Better prediction accuracy using human <em>in vivo</em> Ki</td>
</tr>
<tr>
<td></td>
<td>Customize using in–house data</td>
<td>○</td>
<td></td>
<td>Register in–house compound data</td>
</tr>
<tr>
<td><strong>Extention</strong></td>
<td><strong>in vivo Ki predicted from <em>in vitro</em> Ki</strong></td>
<td>○</td>
<td></td>
<td>Better prediction for compounds w/ high logP when only <em>in vitro</em> Ki is available</td>
</tr>
<tr>
<td></td>
<td>Inhibition of Intestinal Metabolism</td>
<td>○</td>
<td></td>
<td>Verify risk due to inhibition of intestinal metabolism</td>
</tr>
<tr>
<td><strong>Operation</strong></td>
<td><strong>Dosing regimen settings</strong></td>
<td>○</td>
<td></td>
<td>Minimize risk by adjusting the dosing regimen of the substrate and inhibitor</td>
</tr>
<tr>
<td></td>
<td><strong>Batch simulation of multiple drug pairs</strong></td>
<td>○</td>
<td></td>
<td>Run multiple simulations at one time</td>
</tr>
<tr>
<td></td>
<td><strong>Visualize prediction results</strong></td>
<td>○</td>
<td></td>
<td>Visualize the changes in plasma concentration profile</td>
</tr>
</tbody>
</table>
2. Demonstration

Basic Flow of Simulations

1. Add/Edit Drug PK data
2. Choose a Simulation Model
3. Select Substrate/Inhibitor
4. Set Dosing Regimen
5. Run Simulations
6. Confirm Results

Competitive Inhibition
Competitive inhibition is a form of enzyme inhibition where binding of the inhibitor to the enzyme prevents binding of the substrate, but not vice versa.

Mechanism-based Inhibition
Mechanism-based inhibition of an enzyme due to its catalysis of the reaction of an artificial substrate, also called suicide inhibition.

Substrates
- 1. Acipimox
- 2. Nicotinamide
- 3. Chlorpropamide
- 4. Cyclosporine
- 5. Desipramine
- 6. Diazepam
- 7. Oxazepam
- 8. Phenobarbital
- 9. Phenylbutazone
- 10. Phenytoin
- 11. Propranolol

Inhibitors
- 1. Aripiprazole
- 2. Azithromycin
- 3. Clonazepam
- 4. Flurbiprofen
- 5. Flecainide
- 6. Haloperidol
- 7. Procainamide
- 8. Quinidine
2-1 Demonstration 1 (Substrate)

**Objective**

Predict the extent of DDI between a given compound (DrugX) with a known inhibitor

**Conditions**

1. DrugX data available from in vitro and animal studies
2. DrugX is a CYP3A4 substrate
3. Coadministration with Ketoconazole (3A4 inhibitor)
   Ketoconazole clinical dose is 200mg (DDI Simulator)
2–1 Demonstration 1 (Substrate)

Known experimental data

(1) Rat data

- Octanol–water partition coef.: \( \log P = 2.5 \)
- Plasma unbound fraction: \( f_{u,p} = 0.3 \)
- Blood–plasma conc. ratio: \( R_b = 2.4 \)
- Renal clearance: \( CL_r = 0.03 \text{ L/h} \)
- Volume of distribution: \( V_d = 1.0 \text{ L/kg} \)
- Absorption rate constant: \( k_a = 0.8 \text{ (h}^{-1}\text{)} \)

(2) \textit{in vitro} data

- Metabolised by CYP3A4 only: \( f_{m,3A4} = 1.0 \)
- Hepatic intrinsic clearance: \( CL_{h,int} = 57.9 \text{ L/h} \)

(3) Ketoconazole dosing regimen

- Once a day
- Dose: 200mg
DrugX parameters calculated from experimental data and registered in DDI Simulator.

Parameter Calculation Sheet

Experimental Data Input

Automatically Calculated Parameters
# 2-1 Demonstration 1 (Substrate)

## Single Dose Simulation (Competitive Inhibition Model)

### Substrate / Inhibitor Selection

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Atorvastatin</td>
<td>23 Azithromycin</td>
</tr>
<tr>
<td>2 Atorvastatin</td>
<td>24 Cimetidine</td>
</tr>
<tr>
<td>3 Atorvastatin</td>
<td>25 Fluconazole</td>
</tr>
<tr>
<td>4 Atorvastatin</td>
<td>26 Fluoxetine</td>
</tr>
<tr>
<td>5 Desipramine</td>
<td>27 Fluvoxamine</td>
</tr>
<tr>
<td>6 Dexamethasone</td>
<td>28 Indinavir</td>
</tr>
<tr>
<td>7 Diazepam</td>
<td>29 Itraconazole</td>
</tr>
<tr>
<td><strong>DrugX</strong></td>
<td><strong>Ketoconazole</strong></td>
</tr>
<tr>
<td>8 Fluvastatin</td>
<td>30 Ketoconazole</td>
</tr>
<tr>
<td>9 Glimepiride</td>
<td>31 Propafenone</td>
</tr>
<tr>
<td>10 Haloperidol</td>
<td>32 Quinidine</td>
</tr>
</tbody>
</table>

**DrugX and Ketoconazole pair**

### Results (in vitro Ki)

- **AUC ratio**: 1.4
- **Cmax ratio**: 1.3

### Results (in vivo Ki)

- **AUC ratio**: 1.9
- **Cmax ratio**: 1.4

## Dosing Regimen

<table>
<thead>
<tr>
<th>DrugX</th>
<th>Ketoconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose [mg]</strong></td>
<td><strong>Dose [mg]</strong></td>
</tr>
<tr>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td><strong>No. of times per day</strong></td>
<td><strong>No. of times per day</strong></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>No. of days</strong></td>
<td><strong>No. of days</strong></td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
2-1 Demonstration 1 (Substrate)

Repeated Dose Simulation (Competitive Inhibition Model)

Dosing Regimen

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>DrugX</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Dose [mg]</td>
<td>Dose [mg]</td>
</tr>
<tr>
<td>100</td>
<td>200</td>
</tr>
<tr>
<td>No. of times per day</td>
<td>No. of times per day</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>No. of days</td>
<td>No. of days</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
</tr>
</tbody>
</table>

Substrate Timing
Start at 0 [h] after inhibitor dose number

Results (*in vivo* Ki)

- AUC ratio 1.9 → 2.1
- Cmax ratio 1.4 → 1.6

Higher risk of DDI compared to single dose
Investigate the possibility of DrugY as MBI after observing an increase in its inhibitory effect due to preincubation.

Objective

Conditions

(1) DrugY as a CYP2D6 substrate also irreversibly inhibits CYP2D6 (DrugY’s effective blood concentration is assumed to be 30µg/L)

(2) DrugY’s PK parameters have been calculated from in vitro assays and animal data

(3) Coadministration with Metoprolol (2D6 substrate)
## Parameters used in simulation

### (1) Calculated parameters

- **renal clearance**: \( \text{CLr} = 0.728 \text{ L/h} \)
- **volume of distribution**: \( \text{Vd} = 1067 \text{ L/kg} \)
- **plasma unbound fraction**: \( \text{fu,p} = 0.05 \)
- **blood–plasma conc. ratio**: \( \text{Rb} = 1.0 \)
- **absorption rate constant**: \( \text{ka} = 0.987 (\text{h}^{-1}) \)
- **hepatic intrinsic clearance**: \( \text{CLh,int} = 3773 \mu\text{g/L} \)

### (2) *in vitro* data

- **fraction of 2D6 metabolism**: \( \text{fm}_{2D6} = 0.86 \)
- **apparent inhibition constant**: \( \text{Ki,app} = 118.07 \mu\text{g/L} \)
- **max. inactivation rate constant**: \( \text{Kinact} = 10.2 (\text{h}^{-1}) \)

### (3) Metoprolol dosing regimen

- Twice a day (1 week)
- Dose = 60mg
DrugY parameters to be registered in DDI Simulator

PK parameters in vivo Ki

Parameter registration
Investigation of correct oral dose for DrugY in order to reach its effective blood concentration = 30\(\mu\)g/L

100mg/day repeated for 10 days →

40mg/day repeated for 10 days →

\(\sim 100\ \mu\)g/L

\(\sim 30\ \mu\)g/L
2–2 Demonstration 2 (MBI)

Steady-state Calculations

Metoprolol (Substrate)
- Dose [mg]: 60
- No. of times per day: 2
- No. of days: 7

DrugY (Inhibitor)
- Dose [mg]: 40
- No. of times per day: 1
- No. of days: 13

Substrate Timing
- Start at 0 [h] after inhibitor dose number 3

Ratio of Active Enzymes (REact)

Predicted Results
- AUC ratio 4.8
- Cmax ratio 3.8
3. Future Plans

DDI Simulator Future Enhancements

(1) Transporter model
(2) Data on FDA recommended drugs
(3) PK Parameter calculations
(4) Intravenous dosing simulations
3. Future Plans

PK Parameter Calculations
- Excel-based Tool
- Built-in function

PK Parameter Database
- 37 Drugs
- FDA recommended drugs
- Transporter Inhibitors

Dosing Regimen
- Oral Administration
  - Substrate timing
  - Steady-state of repeated dose
- Intravenous Administration

PBPK Models
- Competitive
- MBI
- Transporter V2.0

version 1.0
version upgrade
### 3. Future Plans (New Drug Data)

List of FDA recommended drugs for study of interactions

<table>
<thead>
<tr>
<th>CYP</th>
<th>Substrate</th>
<th>Inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1A2</td>
<td>Theophylline, Caffeine</td>
<td>Fluvoxamine</td>
</tr>
<tr>
<td>2C8</td>
<td>Rosiglitazone</td>
<td>Montelukast</td>
</tr>
<tr>
<td>2C9</td>
<td>Warfarin, Tolbutamide</td>
<td>Fluconazole, Amiodarone</td>
</tr>
<tr>
<td>2C19</td>
<td>Omeprazole, Lansoprazole</td>
<td>Omeprazole, Fluvoxamine, Moclobemide</td>
</tr>
<tr>
<td>2D6</td>
<td>Desipramine, Atomoxetine, Dextromethorphan</td>
<td>Paroxetine, Quinidine, Fluoxetine</td>
</tr>
<tr>
<td>3A4</td>
<td>Midazolam, Buspirone, Felodipine, Lovastatin, Eletriptan</td>
<td>Atazanavir, Indinavir, Saquinavir, Itraconazole, Nelfinavir, Nefazodone, Ketoconazole, Telithromycin, Clarithromycin</td>
</tr>
<tr>
<td>3A5</td>
<td>Sildenafil, Simvastatin, Triazolam</td>
<td></td>
</tr>
</tbody>
</table>

**Guidance for Industry (draft) - Drug Interaction Studies, September 2006**

**Drugs marked in black**: already included in DDI Simulator  
**Drugs marked in red**: ready for next release
shaping tomorrow with you