Part III: DDI Predictions

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SimulationsPlus Learn More! simulations-plus.com/gastroplus
Let’s not forget ...

In GastroPlus®, the PBPK model is linked to the ACAT™ physiological intestinal model ....

These phenomena:
- are happening simultaneously
- are repeated in each of the compartments of the gastrointestinal tract
... and getting the correct dissolution/absorption is the prerequisite for getting correct PBPK & DDI predictions for oral dosage forms!

Interaction Types

• Steady-state competitive inhibition
• Steady-state time-dependent inhibition
• Steady-state induction
  (may include metabolites effect with simulated perpetrator concentrations)

• Dynamic competitive inhibition
• Dynamic time-dependent inhibition
• Dynamic induction
  (include effect of parent and/or metabolites; include enzymes and transporters)
## DDI Module – Validated PBPK Models:  
**Probe Substrates, Inhibitors, and Inducers**

<table>
<thead>
<tr>
<th>Substance 1</th>
<th>Substance 2</th>
<th>Substance 3</th>
<th>Substance 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alfentanil</td>
<td>Fluconazole</td>
<td>Ketoconazole</td>
<td>Rosiglitazone</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Fluvoxamine</td>
<td>Midazolam</td>
<td>Theophylline</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Gemfibrozil</td>
<td>Omeprazole</td>
<td>Tolbutamide</td>
</tr>
<tr>
<td>Caffeine</td>
<td>Gemfibrozil glucuronide</td>
<td>Phenytoin</td>
<td>Triazolam</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Imipramine</td>
<td>Quinidine</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Desipramine</td>
<td>Itraconazole</td>
<td>Rifampicin</td>
<td>Diltiazem</td>
</tr>
<tr>
<td>Raltegravir</td>
<td>Bupropion</td>
<td>Atazanavir</td>
<td>Dolutegravir</td>
</tr>
</tbody>
</table>
Steady-State Predictions
For clarity, effect of only one inhibitor/inducer is shown in the equation, but with the use of simulated concentrations, the effects of parent compound as well as its metabolites (if they have an effect and their constants are specified) can be included.
Steady-State Prediction – Multiple Perpetrators

\[
\frac{AUC_{inh}}{AUC} = \frac{CL}{CL_{inh}} = \frac{1}{\sum_{E=1}^{\text{NumEnz}} \left( 1 + \frac{I}{K_{iE}^{\text{rev}}} \right) \times \left( 1 + \frac{E_{\text{max},E} \times I}{E_{C_{50},E} + I} \right) + \frac{1}{\sum_{c=1}^{\text{compl}} \frac{I_c}{K_{iE,c}^{\text{rev}}}} + \sum_{t=1}^{\text{TDI}} \frac{k_{\text{inact,E,t}} \times I_t}{1 + \sum_{n=1}^{\text{TDI}} \frac{I_n}{K_{iE,n}^{\text{irrev}}} + I_t}}
\]

With multiple competitive inhibitors this term is expanded:

\[
1 + \sum_{E=1}^{\text{NumEnz}} \left( 1 + \frac{I}{K_{iE}^{\text{rev}}} \right) \times \left( 1 + \frac{E_{\text{max},E} \times I}{E_{C_{50},E} + I} \right) + \sum_{c=1}^{\text{compl}} \frac{I_c}{K_{iE,c}^{\text{rev}}}
\]

With multiple TDI this term is expanded:

\[
1 + \sum_{t=1}^{\text{TDI}} \frac{k_{\text{inact,E,t}} \times I_t}{1 + \sum_{n=1}^{\text{TDI}} \frac{I_n}{K_{iE,n}^{\text{irrev}}} + I_t}
\]
Steady-State Prediction – Multiple Perpetrators

\[
\frac{AUC_{inh}^{\text{inh}}}{AUC} = \frac{CL}{CL_{inh}} = 1 + \sum_{E=1}^{\text{NumEnz}} \left( 1 + \frac{I}{K_{iE}^{\text{rev}}} \right) \times \left( 1 + \frac{k_{\text{inact},E} \times I}{k_{\text{deg},E} (K_{iE}^{\text{irrev}} + I)} \right) + f_{m_{\text{other}}}
\]

With multiple inducers this term is expanded:

\[
\left( 1 + \sum_{d=1}^{\text{inducers}} \frac{E_{\text{max},E,d} \times I_d}{EC_{50,E,d} + I_d} \right)
\]
Steady-State Prediction - Required Inputs

1. $f_m$ and $F_g$ values for substrate
2. $K_i$ (or $IC_{50}$) for inhibitor
3. $K_{inact}$ [$\text{min}^{-1}$] for inhibitor for time-dependent inhibition
4. $EC_{50}$ and $E_{max}$ for inducer
5. Enzyme turnover rate ($k_{deg}$ [$\text{min}^{-1}$]) for time-dependent inhibition and induction
6. Inhibitor/inducer concentration:
   a. Number of different calculated and simulated inhibitor/inducer concentration estimates are available
   b. Full PK model is required for simulated inhibitor/inducer concentration
   c. Additional inputs required for calculated inhibitor/inducer concentrations ($F_a$, $FD_p$, $F$, $k_a$, $k_{el}$, etc.)

$f_m$ - fraction of total gut or total systemic clearance attributed to given enzyme
$F_g$ – fraction of the dose that escapes gut metabolism
Default $k_{deg}$ values for CYPs are included in program
Example: Steady-state DDI predictions

$fm$ calculation from in vitro data in human liver microsomes

• Create a new database under File/New Drug Database menu (name it “Drug1234”)
  Name the 1st record “Drug1234-DDI-HLM”
• Open the DDI Module by going to the Modules (Optional)/8 DDI menu
• Click the Calculate $fm$ values button to launch the $fm$ calculation tool
  Select the tab “microsomes (HLM)”
• Enter the measured un-inhibited $CL_{int}$ of 269 uL/min/mg MP and assume that 10% of the clearance is “non-CYP”
• Enter the information in the table below onto the grid:

<table>
<thead>
<tr>
<th>Inhibitor</th>
<th>Inhibited Enzyme</th>
<th>HLM CL (µL/min/mg MP)</th>
<th>CYP Abundance in HLM (pmol CYP/mg MP)</th>
</tr>
</thead>
<tbody>
<tr>
<td>alpha-naphthoflavone</td>
<td>1A2</td>
<td>240</td>
<td>42</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>2C9</td>
<td>250</td>
<td>32</td>
</tr>
<tr>
<td>Quinidine</td>
<td>2D6</td>
<td>200</td>
<td>9.1</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>3A4</td>
<td>100</td>
<td>78</td>
</tr>
</tbody>
</table>

• Once finished, click the Export $fm$ values button
• Let’s predict steady-state DDIs with fluconazole
Steady-State Prediction - Required Inputs

1. $f_m$ and $F_g$ values for substrate
2. $K_i$ (or $IC_{50}$) for inhibitor
3. $K_{inact}$ [min$^{-1}$] for inhibitor for time-dependent inhibition
4. $EC_{50}$ and $E_{max}$ for inducer
5. Enzyme turnover rate ($k_{deg}$ [min$^{-1}$]) for time-dependent inhibition and induction
6. Inhibitor/inducer concentration:
   a. Number of different calculated and simulated inhibitor/inducer concentration estimates are available
   b. Full PK model is required for simulated inhibitor/inducer concentration
   c. Additional inputs required for calculated inhibitor/inducer concentrations ($Fa$, $FDp$, $F$, $k_a$, $k_{el}$, etc.)

$fm$ - fraction of total gut or total systemic clearance attributed to given enzyme
$Fg$ – fraction of the dose that escapes gut metabolism
Default $k_{deg}$ values for CYPs are included in program
Estimating \( fm \) values from \textit{in vitro} measurements

Calculate substrate’s \( fm \) values from \textit{in vitro} measurements in \textit{rCYP}

- User will enter \textit{in vitro} intrinsic clearances for individual enzymes measured in recombinant system and corresponding ISEFs
- If ISEFs are not available, they may be calculated directly in this tool after entering clearances of standard compound measured in HLM, \textit{rCYP} and entering the abundance of each CYP in HLM used in the \textit{in vitro} assay:

\[
ISEF^{r\text{CYP}} = \frac{\langle \text{Standard CL}_{\text{Lint}} \text{ HLM} \rangle}{\langle \text{Standard CL}_{\text{Lint}} \text{ rCYP} \rangle \times \langle \text{Micros CYP expr [pmol/mg MP]} \rangle}
\]

- \textit{in vivo} intrinsic clearance for each enzyme is calculated as:

\[
CL^{CYP}_{\text{int}} = ISEF^{r\text{CYP}} \times \langle \text{Compound CL}_{\text{Lint}} \text{ rCYP} \rangle \times \langle \text{In Vivo CYP Expr [pmol /mg MP]} \rangle \\
\times \langle \text{mg protein/g tissue} \rangle \times \langle \text{Tissue Weight} \rangle
\]

- \( fm \) value for each enzyme \( i \) is calculated as:

\[
fm^{CYP} = \frac{CL^{CYP}_{\text{int}}}{\sum_{CYP} CL^{CYP}_{\text{int}}} \times \left( 100 - \langle \text{Percent non - CYP CL [%]} \rangle \right)
\]
Estimating $fm$ values from *in vitro* measurements

Calculate substrate’s $fm$ values from *in vitro* measurements in HLM

- User will enter *in vitro* intrinsic clearances measured in HLM without any inhibitors and in the presence of inhibitors specific for individual enzymes and the abundance of each CYP in HLM used in the *in vitro* assay.
- *in vivo* intrinsic clearance for each enzyme is calculated as:

$$CL_{int}^{CYP} = \frac{CL_{HLM}^{int} \times \left(1 - \frac{CL_{int}^{CYP-inhib}}{CL_{HLM}^{int}}\right) \times \langle \text{In Vivo CYP Expr [pmol/mg MP]} \rangle}{\langle \text{Micros CYP Expr [pmol/mg MP]} \rangle} \times \langle \text{mg protein/g tissue} \rangle \times \langle \text{Tissue Weight} \rangle$$

- $fm$ value for each enzyme $i$ is calculated as:

$$fm_{CYP}^{i} = \frac{CL_{int}^{CYP}}{\sum_{CYP} CL_{int}^{CYP}} \times (100 - \langle \text{Percent non - CYP CL [%]} \rangle)$$
Steady-State Prediction - Required Inputs

1. \( f_m \) and \( F_g \) values for substrate
2. \( K_i \) (or \( IC_{50} \)) for inhibitor
3. \( K_{\text{inact}} \ [\text{min}^{-1}] \) for inhibitor for time-dependent inhibition
4. \( EC_{50} \) and \( E_{\text{max}} \) for inducer
5. Enzyme turnover rate (\( k_{\text{deg}} \ [\text{min}^{-1}] \)) for time-dependent inhibition and induction
6. Inhibitor/inducer concentration:
   a. Number of different calculated and simulated inhibitor/inducer concentration estimates are available
   b. Full PK model is required for simulated inhibitor/inducer concentration
   c. Additional inputs required for calculated inhibitor/inducer concentrations (\( F_a, F_{Dp}, F, k_a, k_{el}, \text{etc.} \))

\( f_m \) - fraction of total gut or total systemic clearance attributed to given enzyme
\( F_g \) – fraction of the dose that escapes gut metabolism
Default \( k_{\text{deg}} \) values for CYPs are included in program
In **Perpetrator Parameters** table select **Inhibition/Induction Constant Type**. The type names consist of 4 parts:

1. **Ki**, **IC50** or **EC50** – select Ki or IC50 for inhibition; select EC50 for induction
2. **rev** or **irr** – select **rev** for reversible or competitive inhibition; select **irr** for irreversible or time-dependent inhibition (this selection is applicable only for inhibition and will be available only with Ki and IC50 entries)
3. **in vitro** or **in vivo** – was the value obtained **in vitro** (e.g. microsomes) or **in vivo** (and is calculated based on measured concentration in plasma)
4. **U** or **T** – select **U** for unbound or **T** for total
Steady-State Prediction - Required Inputs

1. $f_m$ and $F_g$ values for substrate
2. $K_i$ (or $IC_{50}$) for inhibitor
3. $K_{\text{inact}} [\text{min}^{-1}]$ for inhibitor for time-dependent inhibition
4. $EC_{50}$ and $E_{\max}$ for inducer
5. Enzyme turnover rate ($k_{\text{deg}} [\text{min}^{-1}]$) for time-dependent inhibition and induction

6. **Inhibitor/inducer concentration:**
   a. Number of different calculated and simulated inhibitor/inducer concentration estimates are available
   b. Full PK model is required for simulated inhibitor/inducer concentration
   c. Additional inputs required for calculated inhibitor/inducer concentrations ($Fa$, $FDp$, $F$, $k_a$, $k_{el}$, etc.)

$f_m$ - fraction of total gut or total systemic clearance attributed to given enzyme
$F_g$ – fraction of the dose that escapes gut metabolism
Default $k_{\text{deg}}$ values for CYPs are included in program
Steady-State – Perpetrator Concentrations

DDI Module within GastroPlus offers number of ways to obtain ‘effective’ perpetrator concentration for prediction under steady-state assumptions

**Calculated** perpetrator concentrations are obtained from standard equations:

### Systemic Average

\[
[I]_{av} = \frac{D}{\tau} \frac{1}{CL / F}
\]

### Systemic Cmin

\[
[I]_{\text{min}} = [I]_{\text{max}} \times e^{-k_e \tau}
\]

### Systemic Cmax

\[
[I]_{\text{max}} = \frac{[I]_{av} k_e \tau}{1 - e^{-k_e \tau}}
\]

### Liver Inlet

\[
[I]_{in} = [I]_{av} + \frac{k_a \times F_D p \times D}{Q_h}
\]

### Gut

\[
[I]_g = \frac{k_a \times F_a \times D}{Q_e}
\]

**Corresponding unbound concentrations are calculated as:**

\[
[I]_U = [I] \times \frac{F_{up} [%]}{100}
\]

*D*-dose, \(\tau\)-dosing interval, \(CL\)-clearance, \(k_e\)-elimination rate constant, \(k_a\)-absorption rate constant, \(F_a\)-fraction absorbed, \(F_D p\)-fraction of dose getting to portal vein, \(F\)-bioavailability, \(Q_h\)-liver blood flow, \(Q_e\)-enterocytic blood flow, \(F_{up} [%]\) – percent of drug unbound in plasma
Steady-State – Perpetrator Concentrations

DDI module within GastroPlus offers number of ways to obtain ‘effective’ perpetrator concentration for prediction under steady-state assumptions

*Simulated* perpetrator concentrations are obtained from simulated profile for perpetrator using full absorption and PK model saved in the database:

- If perpetrator reached steady-state before substrate administration, the plasma or liver effective perpetrator concentration is estimated as an average of simulated peak and trough concentrations.
Steady-State – Perpetrator Concentrations

DDI module within GastroPlus offers number of ways to obtain ‘effective’ perpetrator concentration for prediction under steady-state assumptions

*Simulated* perpetrator concentrations are obtained from simulated profile for perpetrator using full absorption and PK model saved in the database:

- If perpetrator *did not reach steady-state* before substrate administration, the *plasma* or *liver* effective perpetrator concentration is estimated an AUC-driven average concentration across the dosing interval from the time of substrate administration

\[\text{Time of substrate administration} \rightarrow \text{Equivalent AUC}\]
Steady-State – Perpetrator Concentrations

DDI module within GastroPlus offers number of ways to obtain ‘effective’ perpetrator concentration for prediction under steady-state assumptions

*Simulated* perpetrator concentrations are obtained from simulated profile for perpetrator using full absorption and PK model saved in the database:

- **Gut** effective perpetrator concentration is estimated as an average enterocyte concentration across all compartments - for each compartment, the perpetrator concentration is calculated at the time of substrate transit into the compartment based on substrate administration time and compartment transit times
Dynamic Simulations
Dynamic DDI Simulations

Dynamic simulation makes no assumptions or simplifications beyond those already included in the PK models of interacting compounds:

• Accounts for interaction in any tissue
• Accounts for competition between multiple substrates of the same enzyme/transporter and for a possible effect of ‘substrate’ on ‘inhibitor’/’inducer’
  – NOTE: if multiple compounds in the system have specified $K_m$ and $V_{max}$ values for the same enzyme/transporter, their competition for the binding sites of that enzyme/transporter will be accounted for using $K_i = K_m$
• Accounts for competition between multiple irreversible inhibitors for the binding to enzyme
• Accounts for possibility of perpetrator acting as inhibitor and inducer at the same time
• Accounts for auto-induction and auto-inhibition
• Default physiological parameters (expression levels, turnover rates) are available for CYP enzymes, but any enzyme/transporter may be included if user knows relevant parameter values
Dynamic Simulation – Equations

Competitive Inhibition

\[
v = \frac{\text{EnzAct}_0 \times V_{\text{max}} \times [S]_u}{K_m \left(1 + \sum_{j=1}^{N} \frac{[A]_{u,j}}{K_{m,j}} + \sum_{i=1}^{M} \frac{[I]_{u,i}}{K_{i,j}}\right) + [S]_u}
\]

Time-Dependent Inhibition & Induction

\[
\frac{d\text{EnzAct}}{dt} = -\left(\sum_{i=1}^{\text{TDI}} \frac{k_{\text{inact},i} \times [I]_{u,i}}{K_{i,t} \left(1 + \sum_{n=1}^{\text{TDI}} \frac{[I]_{u,n}}{K_{i,n}}\right) + [I]_{u,i}}\right) \times \text{EnzAct} + k_{\text{deg}} \left(\text{EnzAct}_0 - \text{EnzAct}\right)
\]

Multiple substrates of given enzyme
Multiple inhibitors of given enzyme
Multiple inducers of given enzyme
Multiple time dependent inhibitors of given enzyme
Dynamic DDI Simulations – Required Inputs

1. $f_m$ and $F_g$ values for substrate
2. $K_i$ (or IC$_{50}$) for inhibitor
3. $K_{inact}$ [min$^{-1}$] for inhibitor for time-dependent inhibition
4. $EC_{50}$ and $E_{\text{max}}$ for inducer
5. Enzyme turnover rate ($k_{\text{deg}}$ [min$^{-1}$]) for time-dependent inhibition and induction
6. Inhibitor/inducer concentration:
   a. Number of different calculated and simulated inhibitor/inducer concentration estimates are available
   b. Full PK model is required for simulated inhibitor/inducer concentration
   c. Additional inputs required for calculated inhibitor/inducer concentrations (Fa, FDp, F, $k_a$, $k_{el}$, etc.)

Full PK models for perpetrator and victim by themselves (compartmental or PBPK, the same type of model required for both)

NOTE: The physiology for the current record will be used for both compounds
Example: Midazolam - Ketoconazole

Predict DDI interaction between Midazolam and Ketoconazole with the following dosing scheme:

**Ketoconazole:** 400 mg PO dosed once a day (after lunch)

**Midazolam:** 7.5 mg PO dosed 1hr after Ketoconazole on 4th day of Ketoconazole dosing

Competition of Parent and Metabolites for Enzyme Binding Sites

The image shows a diagram illustrating the competition of parent and metabolites for enzyme binding sites. The diagram details the metabolic pathways of omeprazole and its metabolites, including 5-O-desmethylomeprazole, 3-hydroxyomeprazole, and others. The graph on the right compares the concentration over time for different scenarios, showing the impact of interaction on the concentration profiles.
## Itraconazole – Midazolam DDI

(includes inhibitory effect of itraconazole and 3 metabolites)

<table>
<thead>
<tr>
<th>Trial No.</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITZ</td>
<td>50 mg SD</td>
<td>200 mg SD</td>
<td>400 mg SD</td>
<td>200 mg SD</td>
<td>200 mg QD for 6 days</td>
<td>100 mg QD for 4 days</td>
<td>200 mg QD for 6 days</td>
<td>200 mg QD for 4 days</td>
<td>200 mg QD for 4 days</td>
</tr>
<tr>
<td>MID</td>
<td>2 mg PO taken 4 hrs after ITZ</td>
<td>2 mg PO taken 4 hrs after ITZ</td>
<td>2 mg PO taken 4 hrs after ITZ</td>
<td>7.5 mg PO taken 2 hrs after ITZ</td>
<td>0.05 mg/kg IV over 2 min given 2 hrs after ITZ on day 4</td>
<td>7.5 mg PO taken 2 hrs after ITZ on day 4</td>
<td>7.5 mg PO taken 2 hrs after ITZ on day 4</td>
<td>15 mg PO taken 2 hrs after ITZ on day 4</td>
<td>7.5 mg PO taken 1 hr after ITZ on day 4</td>
</tr>
<tr>
<td>Demog (M:F)</td>
<td>n=6 (5:1); 22-42 yrs</td>
<td>n=6 (5:1); 22-42 yrs</td>
<td>n=12 (7.5); 19-25 yrs; 57-95 kg</td>
<td>n=12 (7.5); 19-25 yrs; 57-95 kg</td>
<td>n=12 (4:8); 19-30 yrs; 54-98 kg</td>
<td>n=12 (7.5); 19-25 yrs; 57-95 kg</td>
<td>n=9 (4:5); 22-34 yrs; 55-78 kg</td>
<td>n=9 (2:7); 19-26 yrs; 52-85 kg</td>
<td></td>
</tr>
<tr>
<td>Study Protocol</td>
<td>Not defined - assumed fasted state</td>
<td>Not defined - assumed fasted state</td>
<td>Not defined - assumed fasted state</td>
<td>The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards</td>
<td>The volunteers fasted for 3 hrs before MID administration and had a light standard meal 4 hrs afterwards</td>
<td>The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards</td>
<td>The volunteers fasted for 2 hrs before MID administration and had light standard meals 4 hrs and 7 hrs after MID</td>
<td>The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards</td>
<td></td>
</tr>
</tbody>
</table>

### Midazolam AUC Ratios (updated)

![Graph showing Midazolam AUC Ratios](image_url)

**Legend:**
- Blue bar: Observed
- Red bar: Calculated

**Notes:**
- Demog: n=6 (5:1); 22-42 yrs
- Study Protocol: Not defined - assumed fasted state
Early DDI Risk Assessment – TDIs

- Set of reference drugs for time-dependent inhibition (TDI) of CYP enzymes
  - Literature kinact and Ki used as inputs
- Predicted AUC ratio changes were correctly classified for >80% of drugs
- Have implemented a TDI DDI risk assessment decision tree for drug discovery projects
Regulatory Applications

Updates on FDA’s Drug-Drug Interaction (DDI) Final Guidances

Kellie S. Reynolds, Pharm.D.
Director, Division of Infectious Disease Pharmacology
Xinning Yang, Ph.D.
Policy Lead, Guidance & Policy Team
Office of Clinical Pharmacology (OCP)
Office of Translational Sciences (OTS)
CDER | FDA
April 24, 2020

The views expressed in this presentation are those of the speaker and do not reflect the official policy of the FDA. No official endorsement by the FDA is intended nor should be inferred.

In silico DDI studies

- Physiologically based pharmacokinetic (PBPK) models can replace some clinical studies
- Examples:
  - Impact of weak and moderate CYP2D6 and 3A4 inhibitors
  - Impact of weak and moderate CYP3A4 inducers
- Verify model by comparing clinical and PBPK evaluation: effect of strong perpetrator
- An evolving science
  - New uses are being considered
Recent Approved Drug Product Applications Supported by GastroPlus Simulations

- ALECENSA® (absorption/PPI DDI informing drug labeling)
- BRAFTOVI® (metabolism DDI accepted by regulatory agencies)
- CALQUENCE® (particle size specs accepted by regulatory agencies)
- FARYDAK® (food effect/PPI predictions informing drug labeling)
- INLYTA® (transporter DDI accepted by regulatory agencies)
- KISQALI® (gastric pH predictions accepted by regulatory agencies)
- MEKINIST® (transporter DDI accepted by regulatory agencies)
- MEKTOVI® (metabolism DDI accepted by regulatory agencies)
- OPSUMIT® (particle size specs accepted by regulatory agencies)
- TAMIFLU® (pediatric PBPK predictions informing dose selection)
- ZURAMPIC® (wider product specs accepted by regulatory agencies)
- ... and more!

No other PBBM/PBPK platform has the diversity in applications!