GastroPlus®

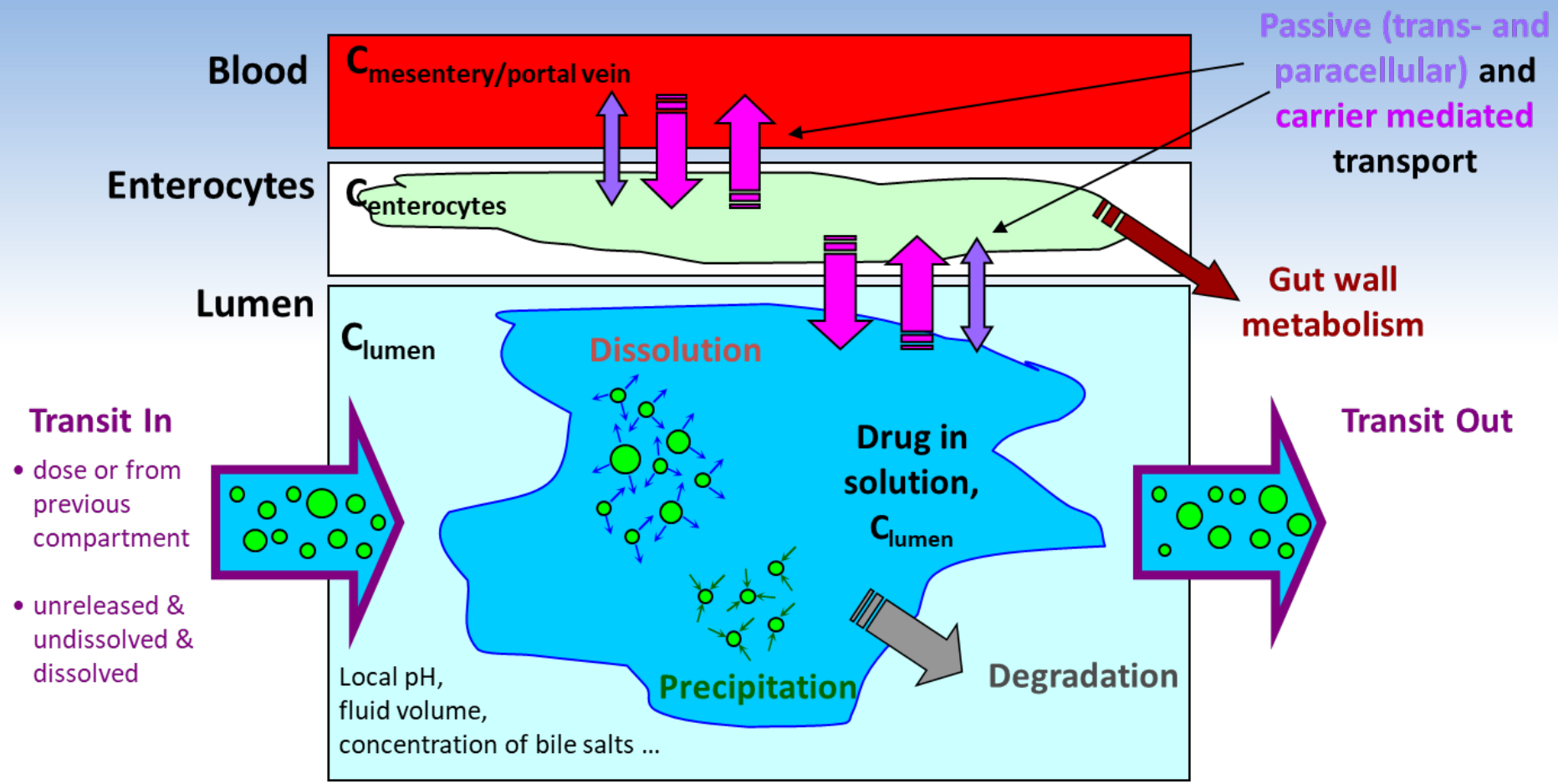
Part III: DDI Predictions

Yujuan Zheng

Viera Lukacova

Let's not forget …

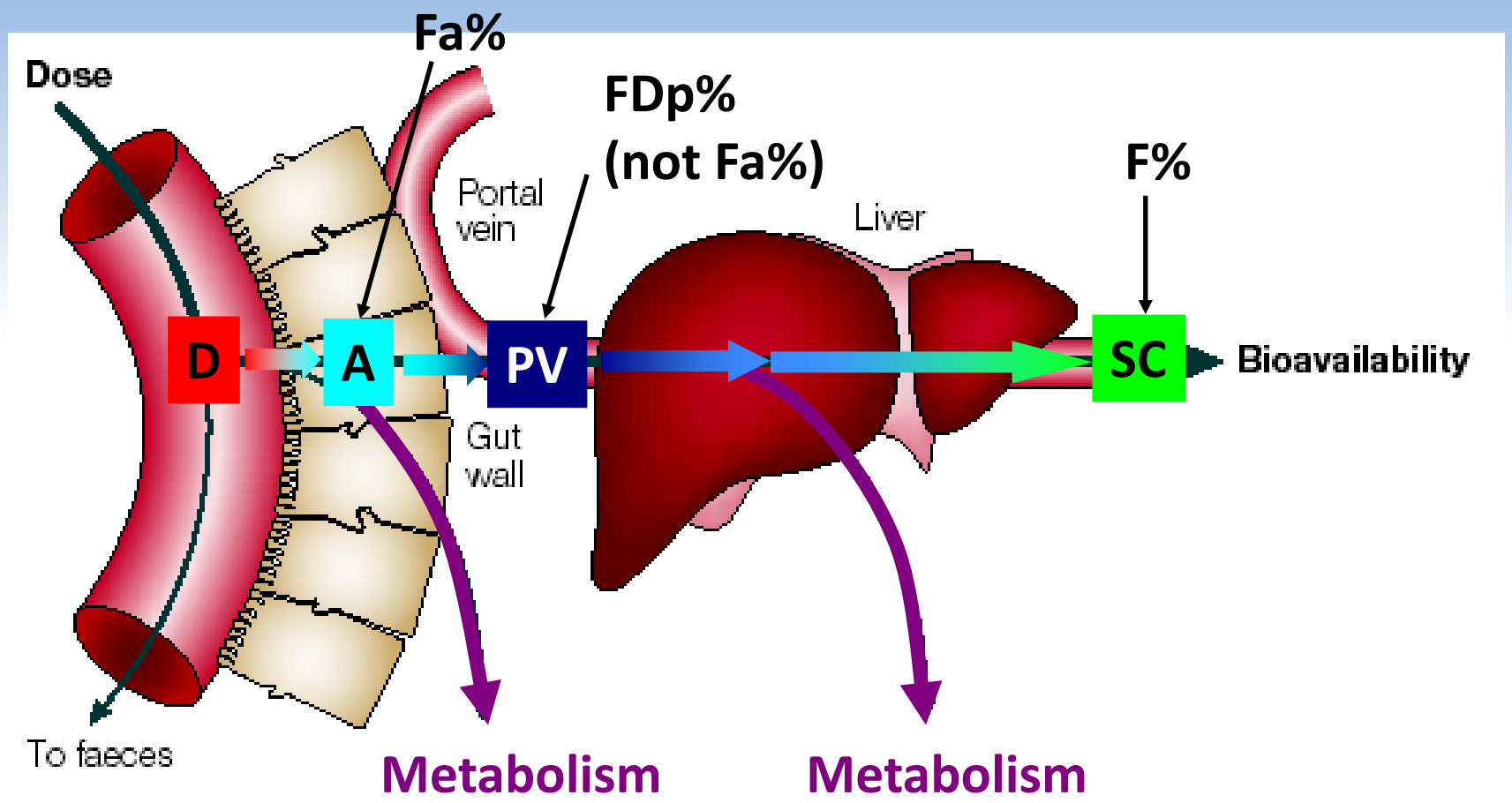
In GastroPlus®, the PBPK model is linked to the ACAT™ physiological intestinal model ….



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!



* Modified from van de Waterbeemd, H, and Gifford, E. *ADMET In Silico Modelling: Towards Prediction Paradise?* Nat. Rev. Drug Disc. 2003, 2:192-204

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

Alfentanil	Fluconazole	Ketoconazole	Rosiglitazone
Atomoxetine	Fluvoxamine	Midazolam	Theophylline
Atomoxetine	Gemfibrozil	Omeprazole	Tolbutamide
Caffeine	Gemfibrozil glucuronide	Phenytoin	Triazolam
Cyclosporine	Imipramine	Quinidine	Warfarin
Desipramine	Itraconazole	Rifampicin	Diltiazem
Raltegravir	Buproprion	Atazanavir	Dolutegravir

Steady-State Predictions

Steady-State Prediction - Equation

contribution of gut to DDI

$$\frac{AUC_{PO}^{inh}}{AUC_{PO}} = \frac{1}{F_g + (1-F_g)\cdot\left(\sum_{E=1}^{NumEnzymes} \frac{fm_E^g \times \left(1+\frac{E_{max}\times I_g}{EC_{50}+I_g}\right)}{\left(1+\frac{I_g}{Ki_E^{rev}}\right)\times\left(1+\frac{k_{inact,E}\times I_g}{k_{deg,E}^g\times\left(Ki_E^{irrev}+I_g\right)}\right)} + fm_{other}^g\right)}$$

$$\times \frac{1}{\left(\sum_{E=1}^{NumEnzymes} \frac{fm_E^L \times \left(1+\frac{E_{max}\times I_L}{EC_{50}+I_L}\right)}{\left(1+\frac{I_L}{Ki_E^{rev}}\right)\times\left(1+\frac{k_{inact,E}\times I_L}{k_{deg,E}^L\times\left(Ki_E^{irrev}+I_L\right)}\right)} + fm_{other}^L\right)}$$

contribution of liver to DDI

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.

Wang Y-H., Drug Metab Dispos 2004, 32:259-266
Galetin A., Drug Metab Pharmacokinet 2010, 25:28-47

Steady-State Prediction – Multiple Perpetrators

$$\frac{AUC^{inh}}{AUC} = \frac{CL}{CL^{inh}} = \frac{1}{fm_E \times \left(1 + \frac{E_{\max,E} \times I}{EC_{50,E} + I}\right)} + fm_{other}$$

$$\sum_{E=1}^{NumEnz} \left(1 + \frac{I}{Ki_E^{rev}}\right) \times \left(1 + \frac{k_{inact,E} \times I}{k_{\deg,E}(Ki^{irrev} + I)}\right)$$

With multiple competitive inhibitors this term is expanded:

$$\left(1 + \sum_{c=1}^{compI} \frac{I_c}{Ki_{E,c}^{rev}}\right)$$

With multiple TDI this term is expanded:

$$1 + \sum_{t=1}^{TDI} \frac{k_{inact,E,t} \times I_t}{k_{\deg,E}\left(Ki_{E,t}^{irrev}\left(1 + \sum_{\substack{n=1 \\ n \neq t}}^{TDI} \frac{I_n}{Ki_{E,n}^{irrev}}\right) + I_t\right)}$$

Steady-State Prediction – Multiple Perpetrators

$$\frac{AUC^{inh}}{AUC} = \frac{CL}{CL^{inh}} = \frac{1}{\sum_{E=1}^{NumEnz} \frac{fm_E \times \left(1 + \frac{E_{\max,E} \times I}{EC_{50,E} + I}\right)}{\left(1 + \frac{I}{Ki_E^{rev}}\right) \times \left(1 + \frac{k_{inact,E} \times I}{k_{\deg,E}(Ki^{irrev} + I)}\right)} + fm_{other}}$$

With multiple inducers this term is expanded:

$$\left(1 + \sum_{d=1}^{inducers} \frac{E_{\max,E,d} \times I_d}{EC_{50,E,d} + I_d}\right)$$

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} [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

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 CLint 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:

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

- 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
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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 *in vitro* measurements

Calculate substrate's *fm* values from *in vitro* measurements in **rCYP**

- User will enter *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, rCYP and entering the abundance of each CYP in HLM used in the *in vitro* assay:

$$ISEF^{rCYP} = \frac{\langle \text{Standard CLint HLM} \rangle}{\langle \text{Standard CLint rCYP} \rangle \times \langle \text{Micros CYP expr [pmol/mg MP]} \rangle}$$

- *in vivo* intrinsic clearance for each enzyme is calculated as:

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

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

$$fm^{CYP} = \frac{CL_{\text{int}}^{CYP}}{\sum_{CYP} CL_{\text{int}}^{CYP}} \times \left(100 - \langle \text{Percent non - CYP CL [\%]} \rangle\right)$$

Proctor N.J., Xenobiotica 2004, 34:151-178

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:

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

$$\times \langle \text{mg protein/g tissue} \rangle \times \langle \text{Tissue Weight} \rangle$$

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

$$fm^{CYP} = \frac{CL_{\text{int}}^{CYP}}{\sum_{CYP} CL_{\text{int}}^{CYP}} \times \left(100 - \langle \text{Percent non - CYP CL [\%]} \rangle\right)$$

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} [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.)

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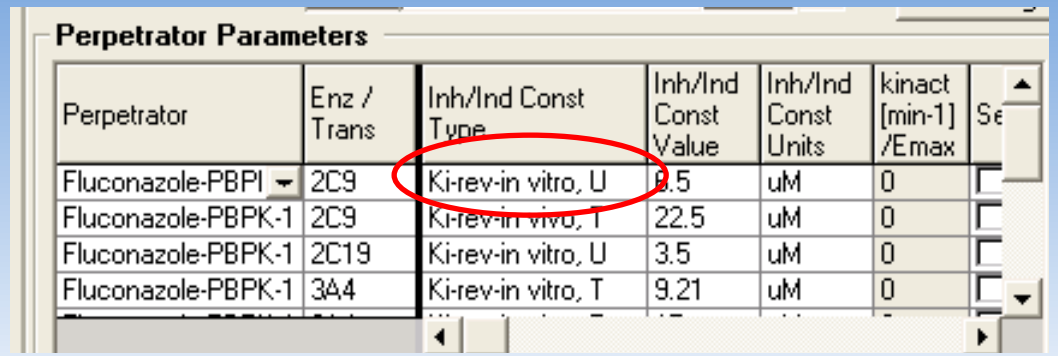
Fg – fraction of the dose that escapes gut metabolism
Default k_{deg} values for CYPs are included in program

How to Specify the Type of Interaction



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_{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
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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

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

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

Systemic Cmin

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

Systemic Cmax

$$[I]_{max} = \frac{[I]_{av} k_{el} \tau}{1 - e^{-k_{el}\tau}}$$

Liver Inlet

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

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, τ-dosing interval, *CL*-clearance, k_{el}-elimination rate constant, k_a-absorption rate constant, *Fa*-fraction absorbed, *FDp*-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

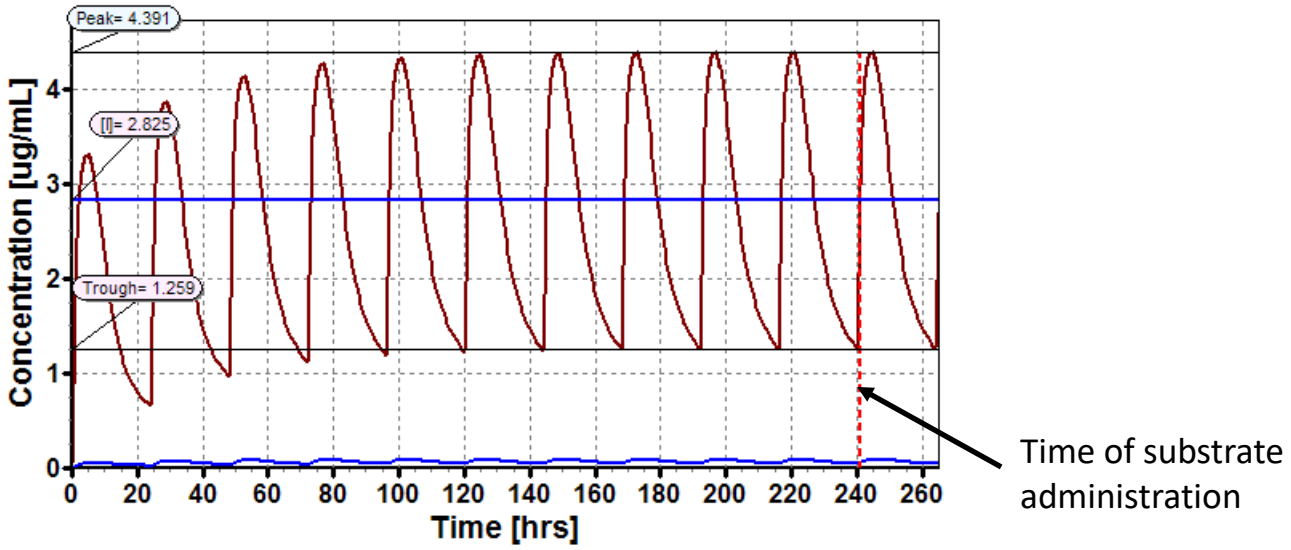
Ito K. Br J Clin Pharmacol 2004, 57(4): 473-486

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

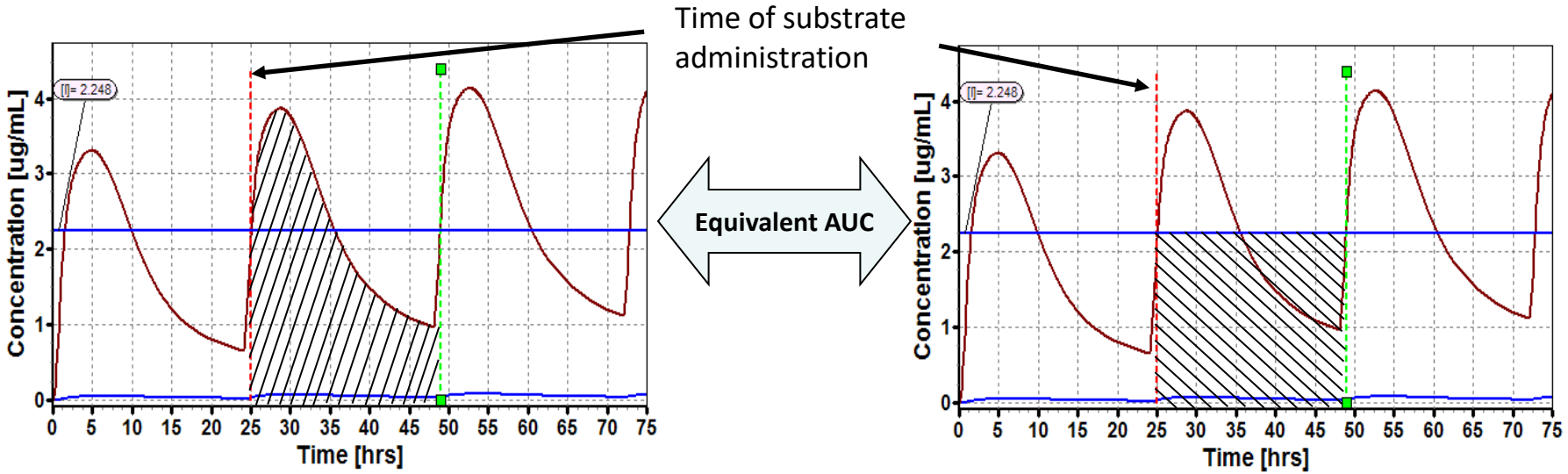


Steady-State – Perpetrator Concentrations

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



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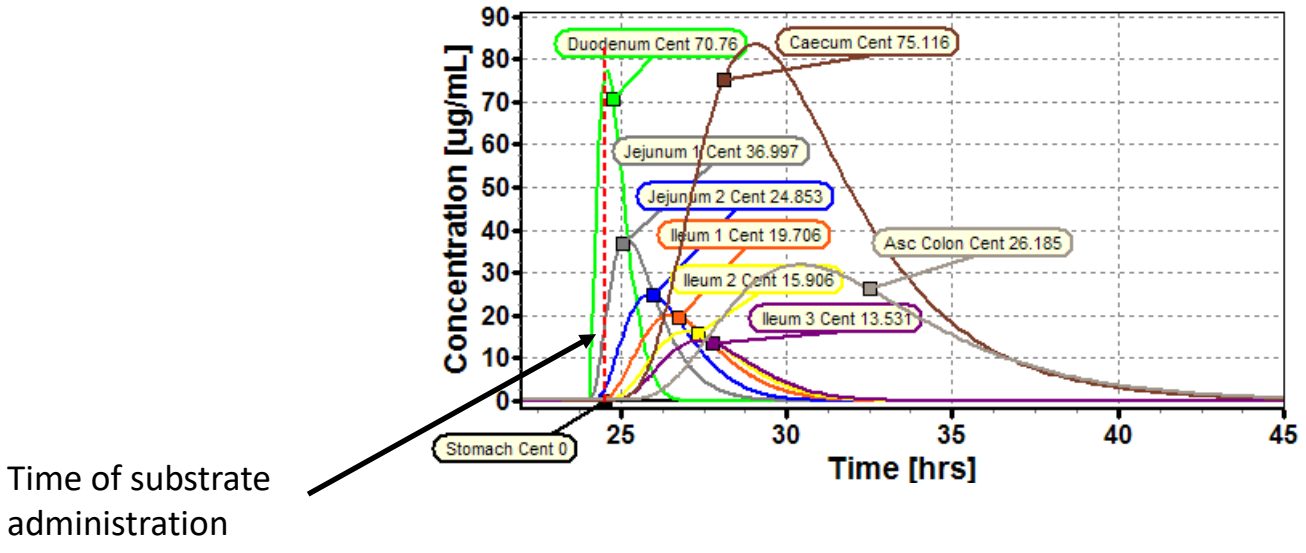
SCIENCE + SOFTWARE = SUCCESS

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



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Q&A

Questions & Answers

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Dynamic Simulations

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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

$$v = \frac{EnzAct_0 \times V_{max} \times [S]_u}{K_m\left(1 + \sum_{j=1}^{N} \frac{[A]_{u,j}}{K_{m,j}} + \sum_{i=1}^{M} \frac{[I]_{u,i}}{K_{i,j}}\right) + [S]_u}$$

multiple substrates of given enzyme

multiple inhibitors of given enzyme

Time-Dependent Inhibition & Induction

$$\frac{dEnzAct}{dt} = -\left(\sum_{t=1}^{TDI} \frac{k_{inact,t} \times [I]_{u,t}}{K_{i,t}\left(1 + \sum_{\substack{n=1 \\ n \neq t}}^{TDI} \frac{[I]_{u,n}}{K_{i,n}}\right) + [I]_{u,t}}\right) \times EnzAct + k_{\deg}\left(EnzAct_0 - EnzAct\right)$$

multiple time dependent inhibitors of given enzyme

multiple inducers of given enzyme

$$+ k_{\deg} \times EnzAct_0 \times \sum_{d=1}^{inducers} \frac{E_{\max,d} \times [I]_u}{EC_{50,d} + [I]_u}$$

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_{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.)~~

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

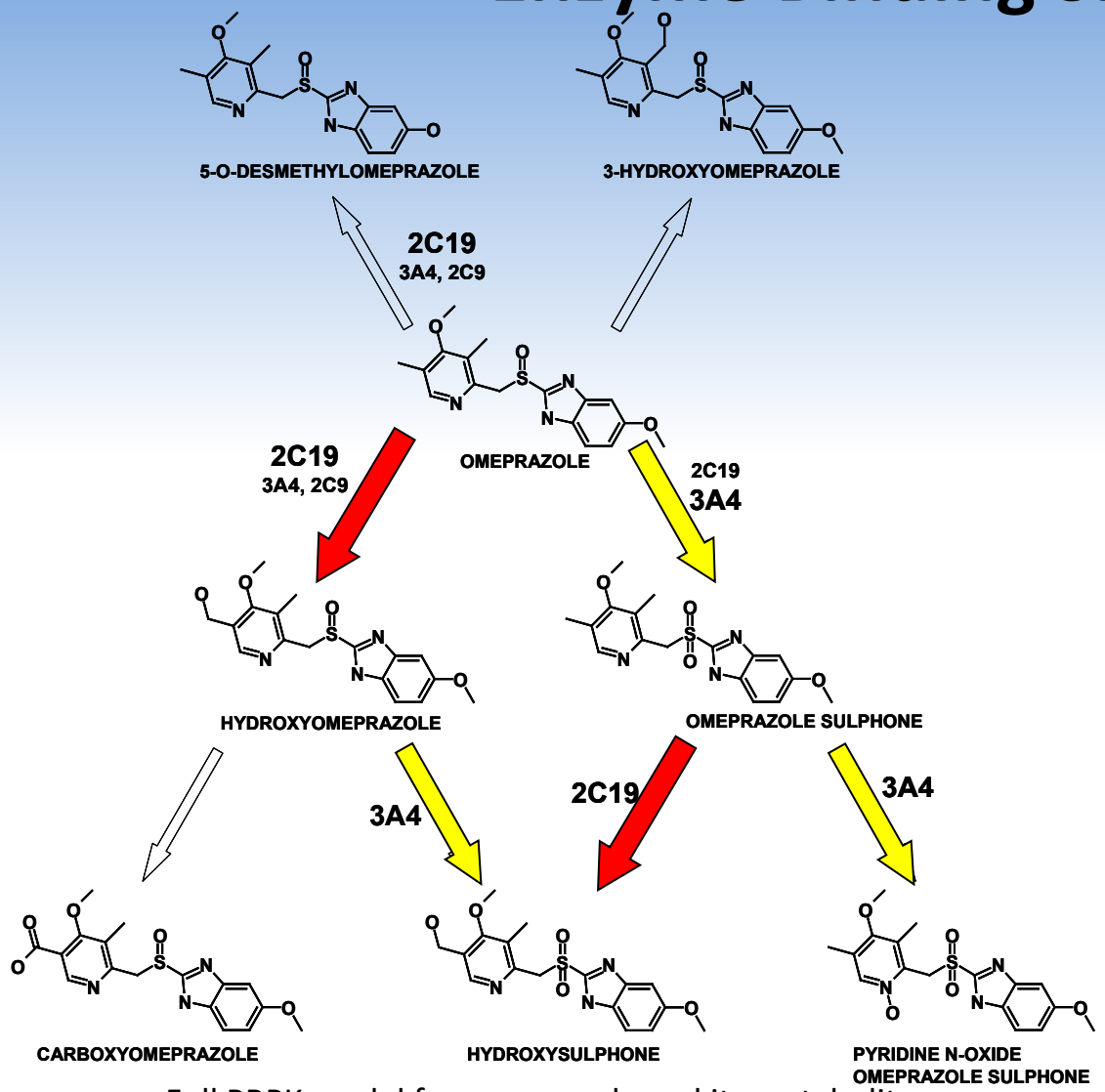
Predict DDI interaction between Midazolam and Ketoconazole with the following dosing scheme:

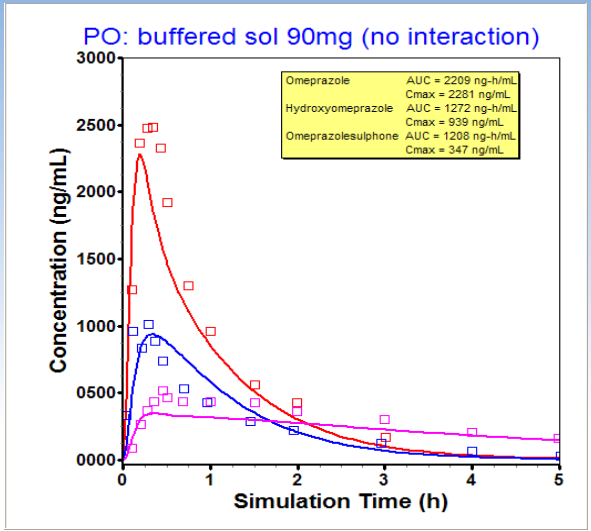
Ketoconazole: 400 mg PO dosed once a day (after lunch)

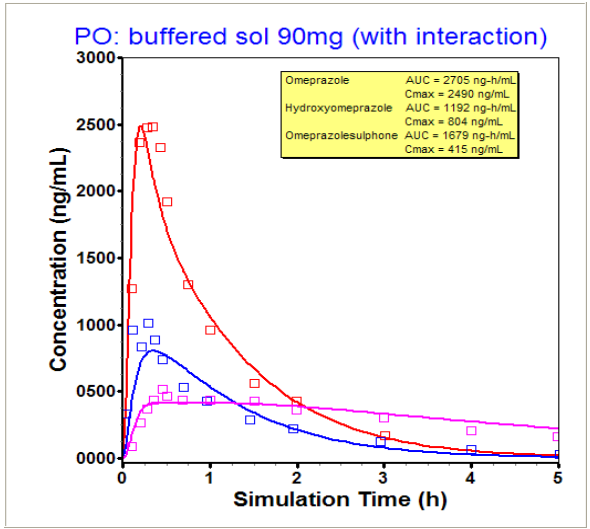
Midazolam: 7.5 mg PO dosed 1hr after Ketoconazole on 4th day of Ketoconazole dosing

Gueorguieva I, J Pharmacokinet Pharmacodyn 2004, 31: 269-298
Bjorkman S, J Pharm Sci 1996, 85: 887-889
Lu Ch, Drug Metab Dispos 2006, 34: 1600-1605, Poulin P, J Pharm Sci 2002, 91: 129-156

Competition of Parent and Metabolites for Enzyme Binding Sites



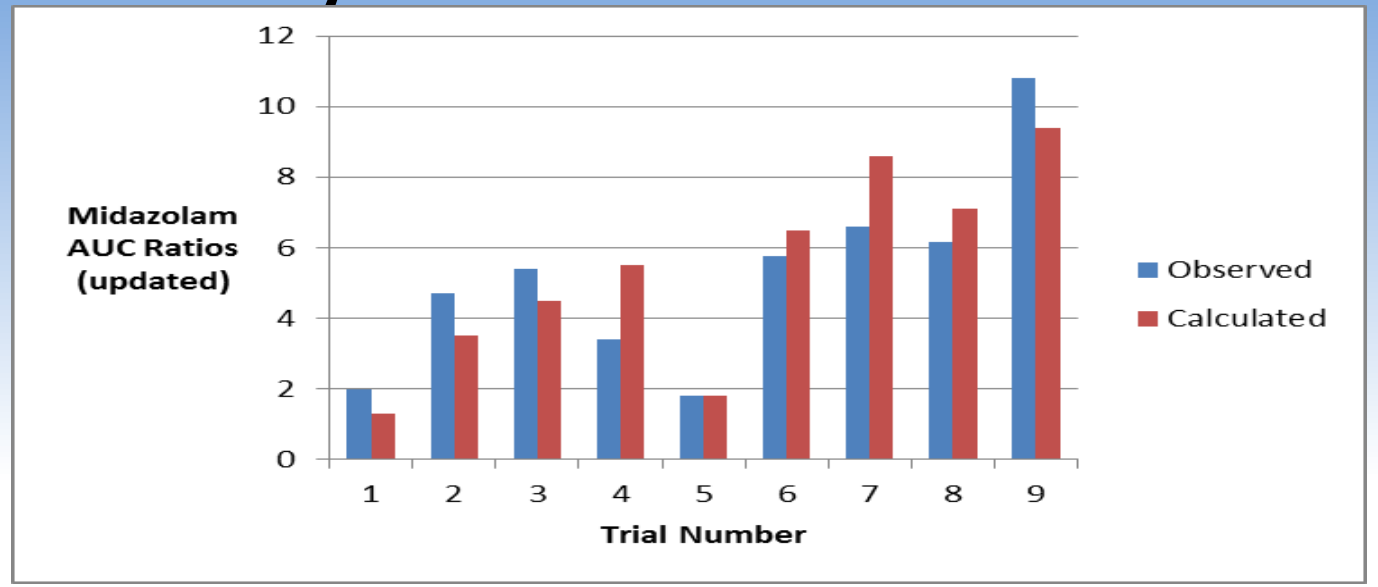




Full PBPK model for omeprazole and its metabolites

Lukacova V. poster ADMET Europe 2010

Itraconazole – Midazolam DDI
(includes inhibitory effect of itraconazole and 3 metabolites)



Trial No.	1	2	3	4	5	6	7	8	9
ITZ	50 mg SD	200 mg SD	400 mg SD	200 mg SD	200 mg QD for 6 days	100 mg QD for 4 days	200 mg QD for 6 days	200 mg QD for 4 days	200 mg QD for 4 days
MID	2 mg PO taken 4 hrs after ITZ	2 mg PO taken 4 hrs after ITZ	2 mg PO taken 4 hrs after ITZ	7.5 mg PO taken 2 hrs after ITZ	0.05 mg/kg IV over 2 min given 2 hrs after ITZ on day 4	7.5 mg PO taken 2 hrs after ITZ on day 4	7.5 mg PO taken 2 hrs after ITZ on day 6	15 mg PO taken 2 hrs after ITZ on day 4	7.5 mg PO taken 1 hr after ITZ on day 4
Demog (M:F)	n=6 (5:1); 22-42 yrs	n=6 (5:1); 22-42 yrs	n=6 (5:1); 22-42 yrs	n=12 (7:5); 19-25 yrs; 57-95 kg	n=12 (7:5); 19-25 yrs; 57-95 kg	n=12 (4:8); 19-30 yrs; 54-98 kg	n=12 (7:5); 19-25 yrs; 57-95 kg	n=9 (4:5); 22-34 yrs; 55-78 kg	n=9 (2:7); 19-26 yrs; 52-85 kg
Study Protocol	Not defined - assumed fasted state	Not defined - assumed fasted state	Not defined - assumed fasted state	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards	The volunteers fasted for 3 hrs before MID administration and had a light standard meal 4 hrs afterwards	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards	The volunteers fasted for 2 hrs before MID administration and had light standard meals 4 hrs and 7 hrs after MID	The volunteers fasted for 3 hrs before MID administration and had a standard meal 4 hrs afterwards
Ref	Templeton et al. 2010	Templeton et al. 2010	Templeton et al. 2010	Olkkola et al. 1996	Olkkola et al. 1996	Ahonen et al. 1995	Olkkola et al. 1996	Backman et al. 1998	Olkkola et al. 1994

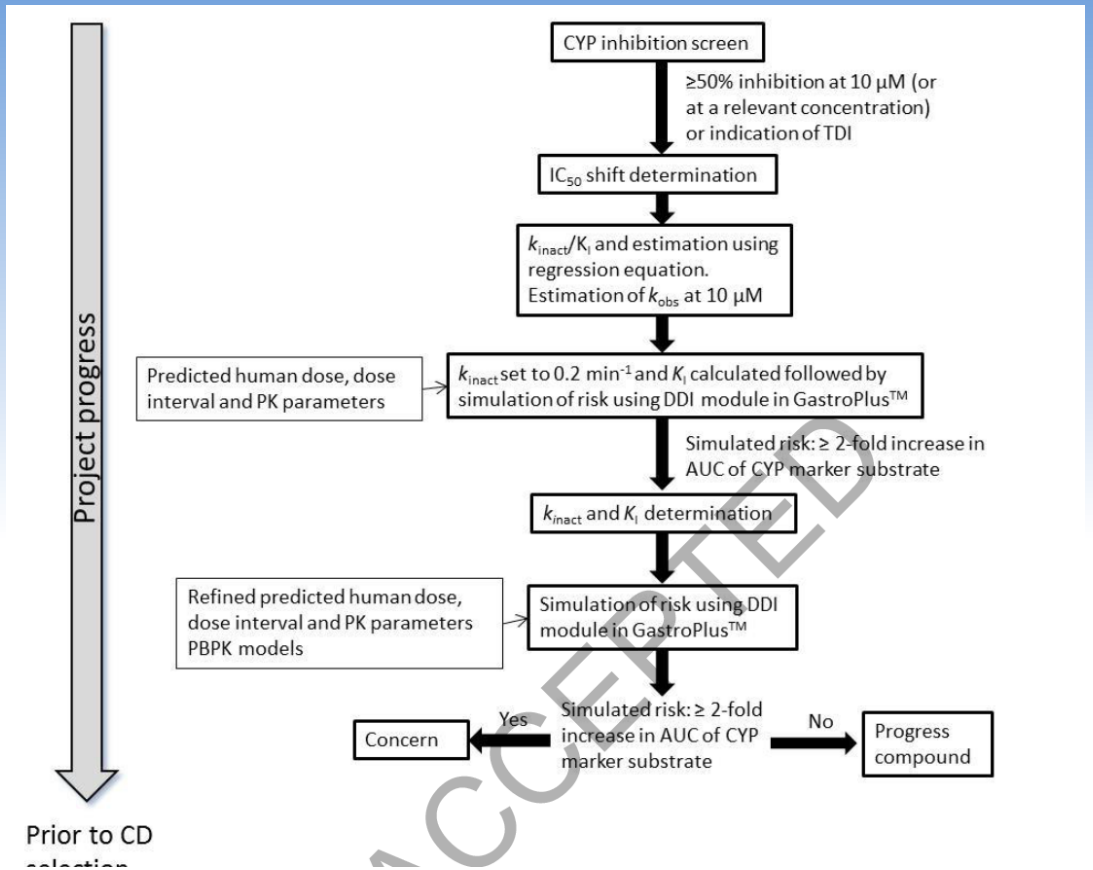
Early DDI Risk Assessment – TDIs

Xenobiotica
the fate of foreign compounds in biological systems

ISSN: 0049-8254 (Print) 1366-5928 (Online) Journal homepage: http://www.tandfonline.com/loi/ixen20

A strategy for early risk predictions of clinical drug-drug interactions involving the GastroPlus™ DDI module for time-dependent CYP inhibitors

Anna-Karin Sohlenius-Sternbeck, Gabrielle Meyerson, Ann-Louise Hagbjörk, Sanja Juric & Ylva Terelius



- 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

Sohlenius-Sternbeck et al., Xenobiotica 2017

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

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

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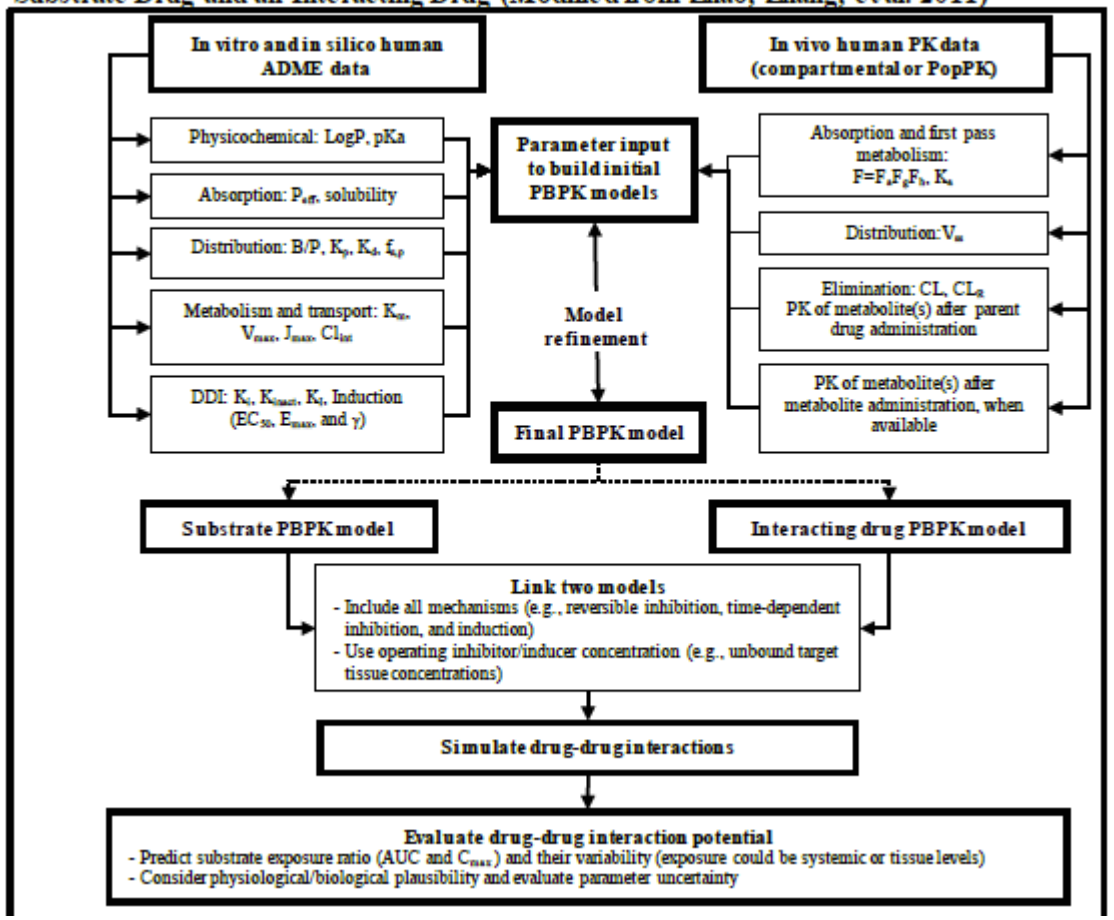
Regulatory Applications

Figure 8. A PBPK Model-Based Framework to Explore the DDI Potential Between a Substrate Drug and an Interacting Drug (Modified from Zhao, Zhang, et al. 2011)*



ADME is the absorption, distribution, metabolism and excretion.
AUC is the area under the plasma concentration versus time curve.
B/P is the blood to plasma ratio.
C_{max} is the maximum concentration.
CL is the clearance.
CL_{int} is the intrinsic clearance.
CL_R is the renal clearance.
DDI is a drug-drug interaction.
EC_{50} is the concentration causing half maximal effect.
E_{max} is the maximum effect.
F is the bioavailability.
F_a is the fraction absorbed.
F_g is the bioavailability in the gut.
F_h is the bioavailability in the liver.
$f_{u,p}$ is the unbound fraction in plasma.
γ is the Hill coefficient.
IC_{50} the concentration causing half maximal inhibition.
I_{max} is the maximum effect or inhibition.
J_{max} is the maximum rate of transporter-mediated efflux/uptake.
K_a is the first-order absorption rate constant.
K_d is the dissociation constant of a drug-protein complex.
K_i is the reversible inhibition constant, concentration causing half maximal inhibition
K_I is the apparent inactivation constant, concentration causing half maximum inactivation
k_{inact} is the apparent maximum inactivation rate constant.
K_m is the Michaelis-Menten constant, substrate concentration causing half maximal reaction or transport
K_p is the tissue to plasma partition coefficient.
LogP is the logarithm of the octanol-water partition coefficient.
MOA is the mechanism of action.
PD is the pharmacodynamics of a drug
P_{eff} is the jejunum permeability.
PK is pharmacokinetics of a drug.
PopPK is population pharmacokinetics.
V is the volume of distribution.
V_{max} is the maximum rate of metabolite formation.

*Note: PBPK models for both substrate and interacting drug (inhibitor or inducer) should be constructed separately using in vitro and in vivo disposition parameters and be verified before they are linked through appropriate mechanisms to predict the degree of DDI.

In vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry, FDA CDER, January 2020

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Q&A

Questions & Answers

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