

Introduction to DDI Simulator

Demonstration of DDI Simulator

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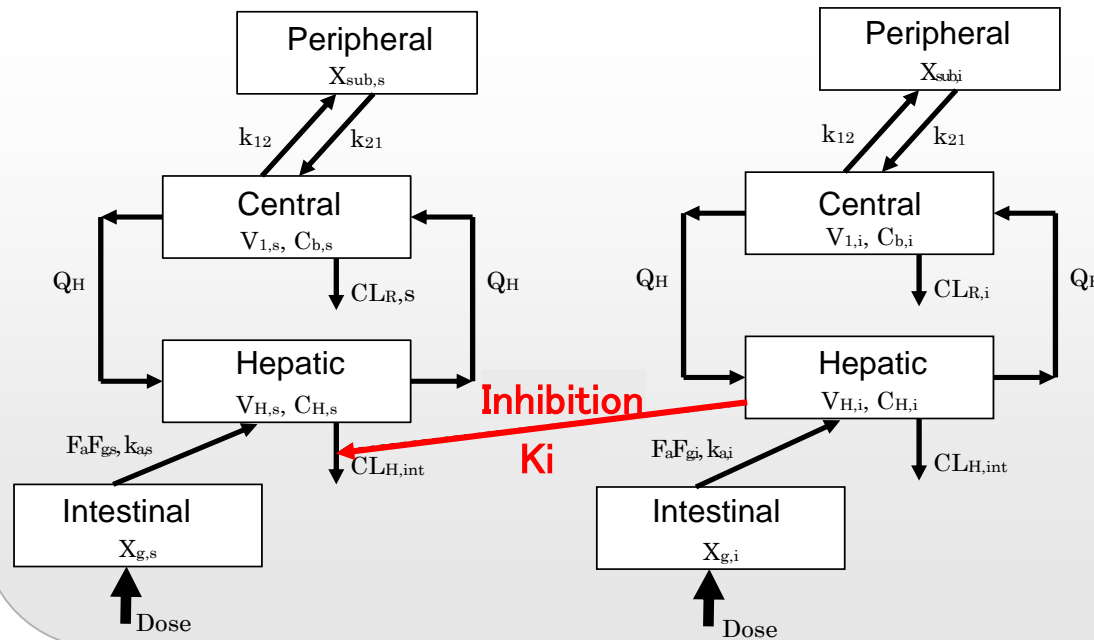
3. Future Plans

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 FUJITSU

Physiologically-based Pharmacokinetic(PBPK) Model



Types of Inhibition

(1) Competitive

[K_i]

(2) Mechanism-based (MBI)

[$K_{i,app}$, 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

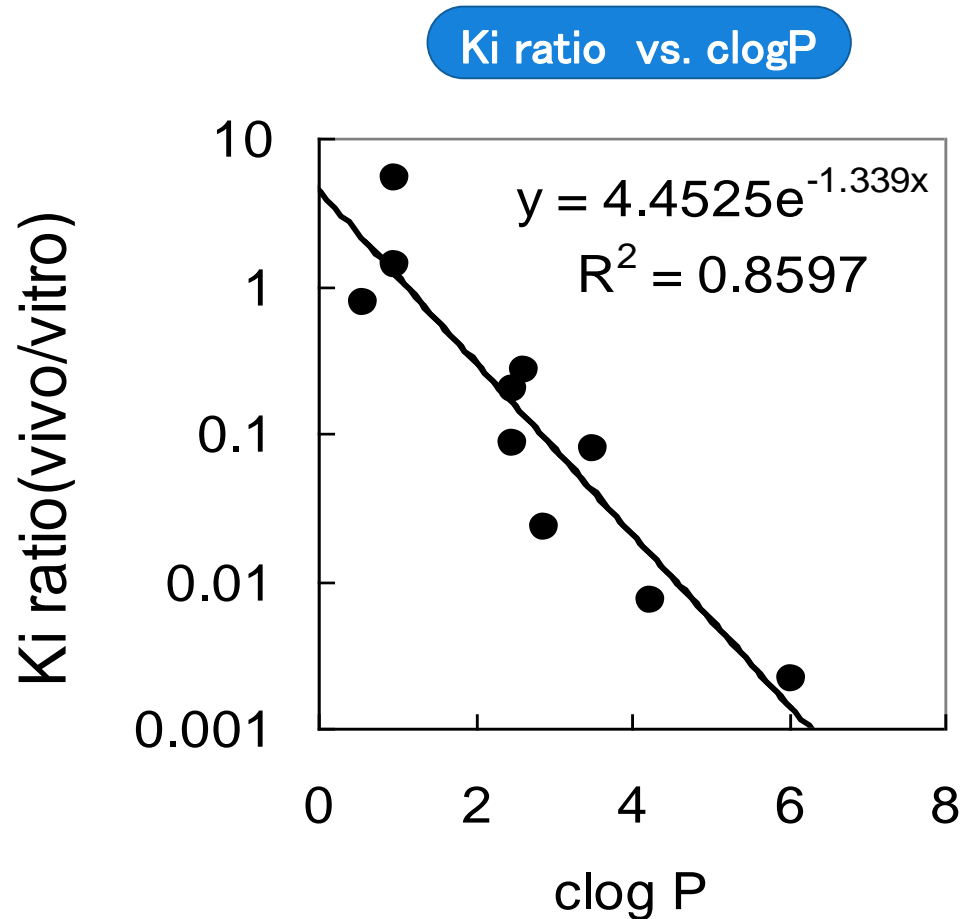
in vivo Ki values were obtained by fitting clinical data

The screenshot shows the DDI Simulator 1.0 interface. On the left, a list of drugs is displayed with columns for ID, Name, and Group. Fluconazole (ID 25) is selected. On the right, a table for inputting Ki values is shown, with columns for *in vitro* Ki and *in vivo* Ki. The *in vitro* Ki values are 2450.2 for 2C9 and 2909.6 for 3A4. The *in vivo* Ki value is 12930 for 2C9 and 5270 for 3A4. A red dashed box highlights the input fields for 2C9 and 3A4 in both the drug list and the Ki table.

	<i>in vitro</i> Ki	<i>in vivo</i> Ki
1A2		
2C8		
2C9	2450.2	12930
2C19		
2D6		
3A4	2909.6	5270
Other		

(3) Approximation of *in vivo* K_i from *in vitro* K_i

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

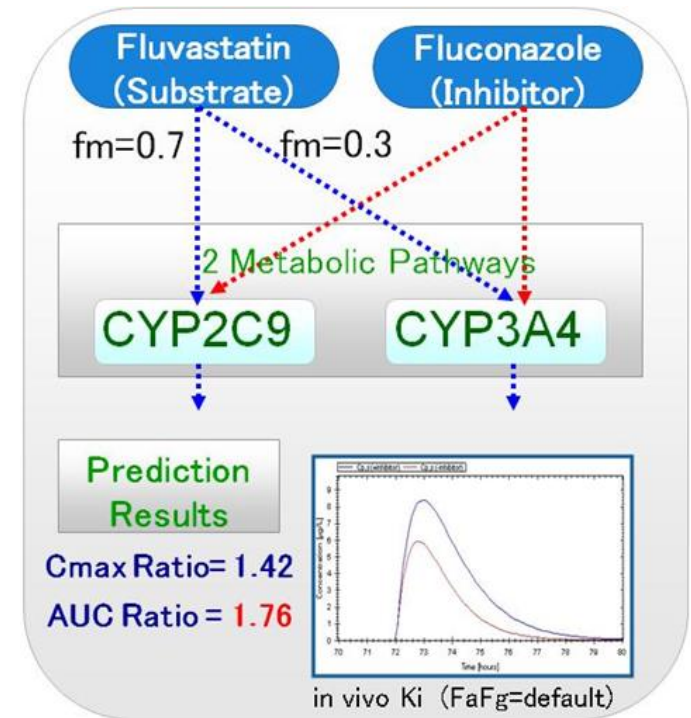


(4) Inhibition of Multiple CYP Isoforms

Only CYP isoforms with fm (fraction of metabolism) values assigned are subject to inhibition

The screenshot shows the 'Inhibitor' tab in the DDI Simulator 1.0 software. The 'fm' (fraction of metabolism) values are set for CYP2C9 (0.7) and CYP3A4 (0.3). Blue callouts point to these values with the text 'CYP2C9 fm' and 'CYP3A4 fm'. A red dashed box highlights the 'Inhibitor' tab and the 'fm' input fields.

CYP Isoform	fm
1A2	
2C8	
2C9	0.7
2C19	
2D6	
3A4	0.3
Other	



(5) Inhibition of Intestinal Metabolism

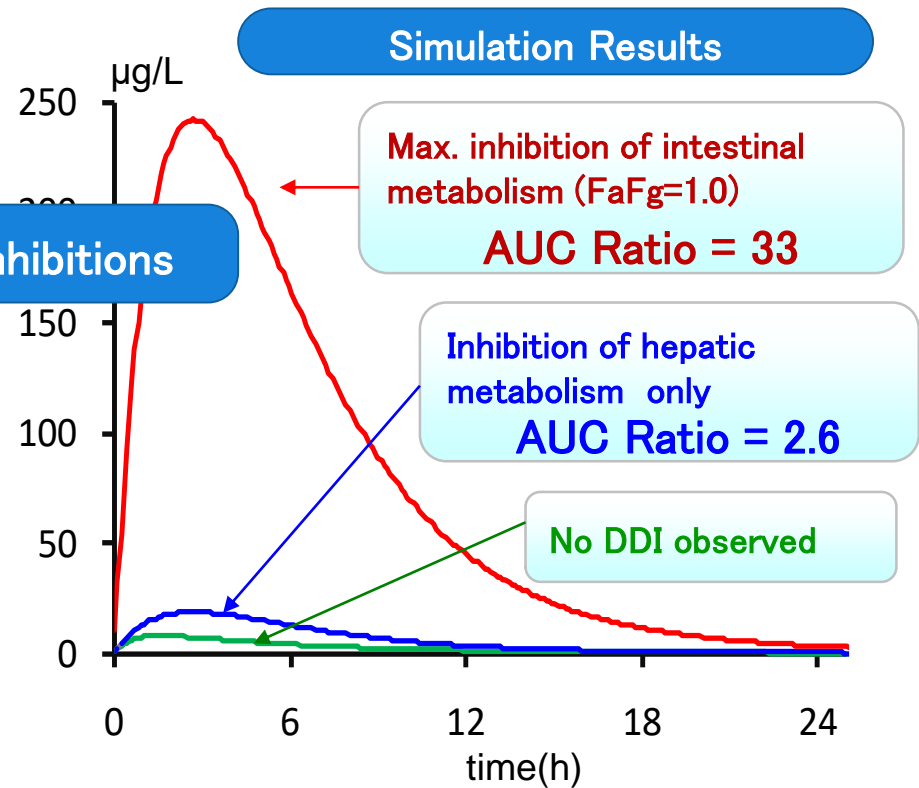
Maximum inhibitions of intestinal metabolisms are considered only for CYP3A4 substrates by automatically setting FaFg to 1

The screenshot shows the 'Simulations' list in DDI Simulator 1.0. Two simulation entries are visible:

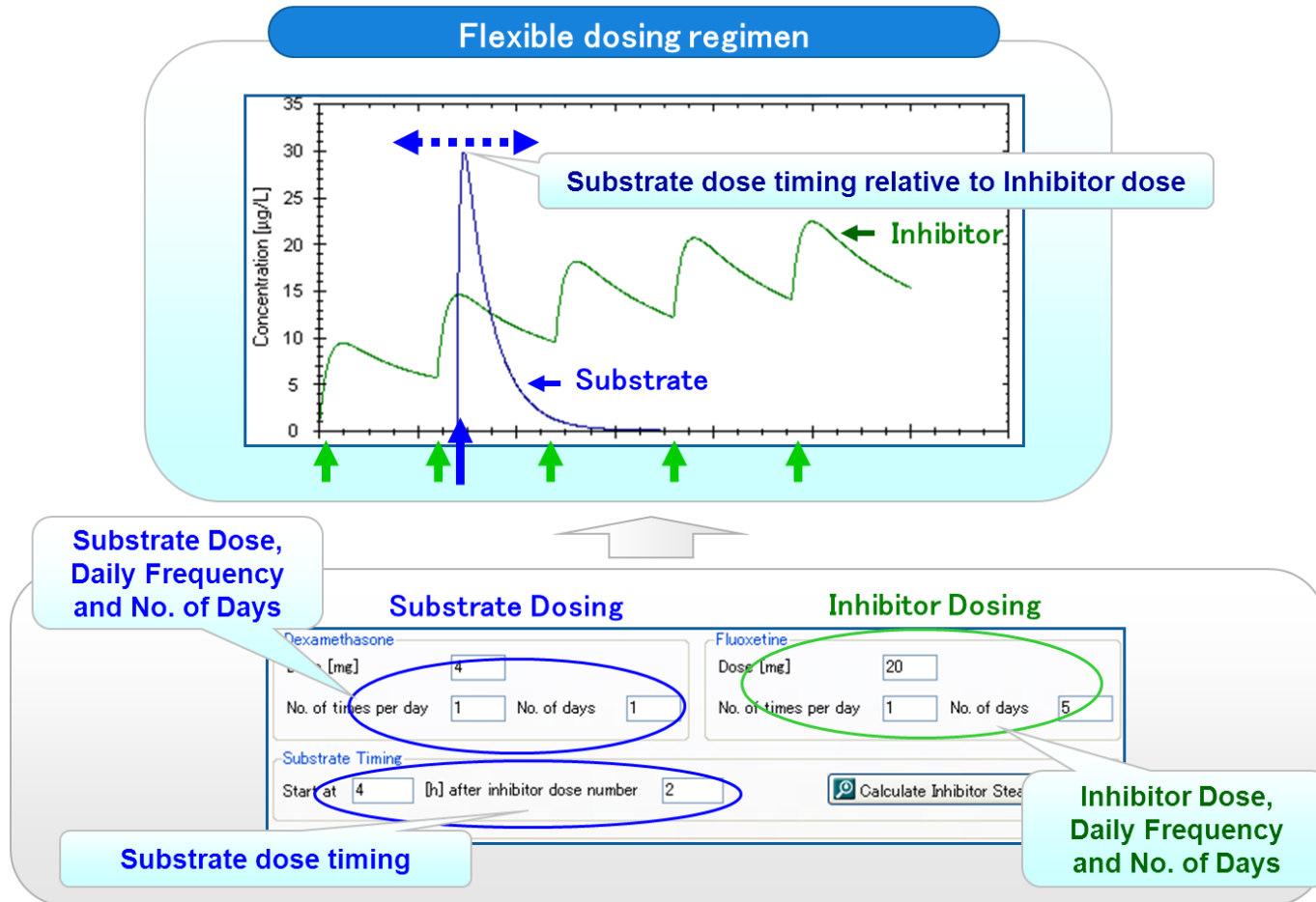
- 110527:173706 (Midazolam, Itraconazole)
 - in vitro Ki
 - predicted in vivo Ki
 - in vivo Ki
 - in vitro Ki, FaFg=1
 - predicted in vivo Ki, FaFg=1
 - in vivo Ki, FaFg=1
- 110527:174555 (Simvastatin, Itraconazole)
 - in vitro Ki
 - predicted in vivo Ki
 - in vivo Ki
 - in vitro Ki, FaFg=1
 - predicted in vivo Ki, FaFg=1
 - in vivo Ki, FaFg=1

A blue callout box labeled 'maximum inhibitions' points to the 'predicted in vivo Ki, FaFg=1' entries for both simulations. A red dashed box highlights the simulation details for the Simvastatin entry, which includes a table of pharmacokinetic parameters:

Parameter	Value
AUC (-D) [µg·h/L]	1,469
AUC (+D) [µg·h/L]	41,987
AUC Ratio	28.593
Cmax (-D) [µg/L]	0.199
Cmax (+D) [µg/L]	5.459
Cmax Ratio	27.402



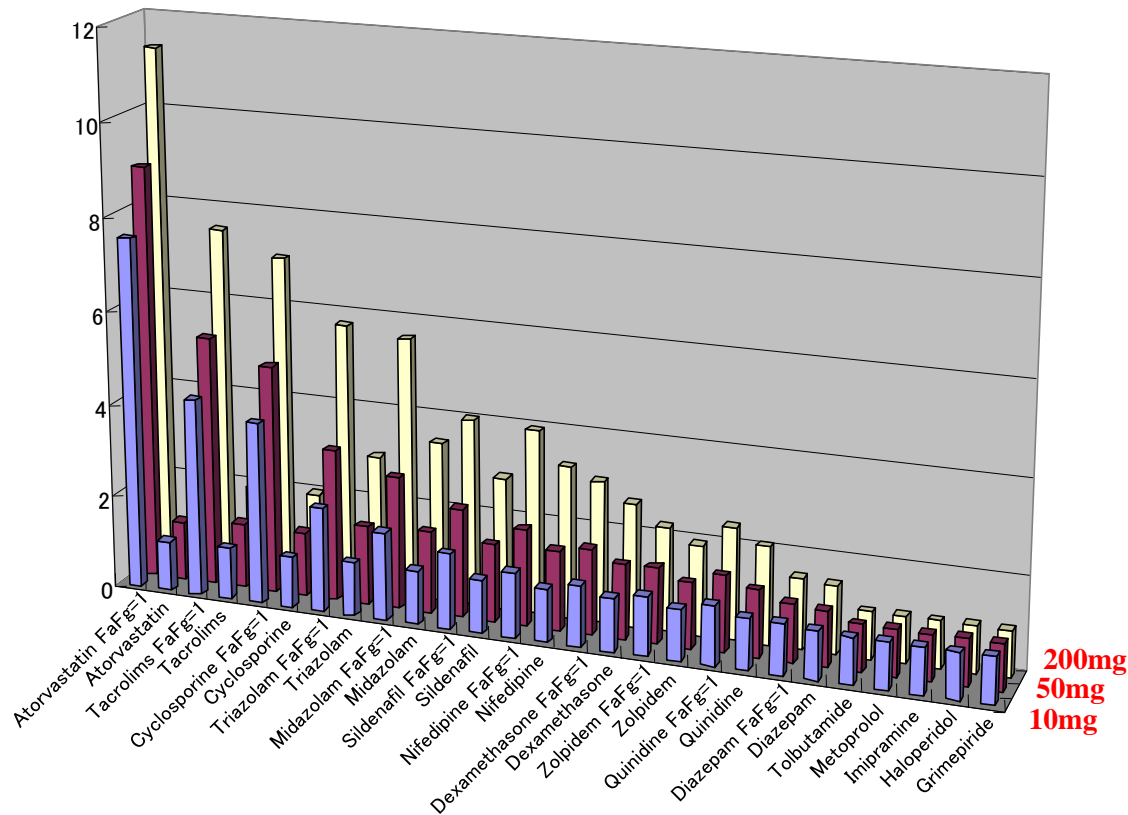
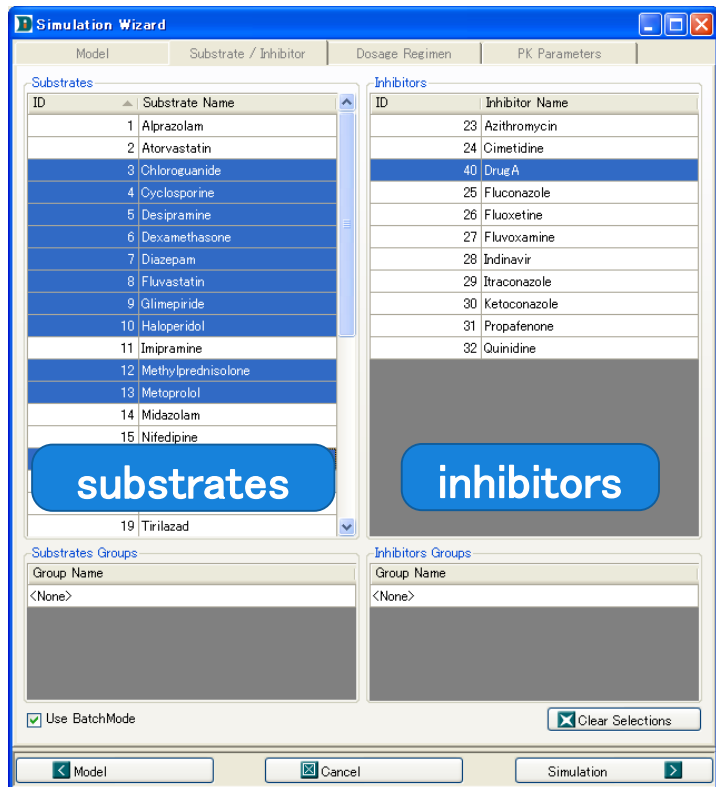
(6) Dosing Regimen Optimization



Minimize DDI risks by adjusting the substrate dose timing and/or frequency

(7) Batch Simulations

AUC ratio

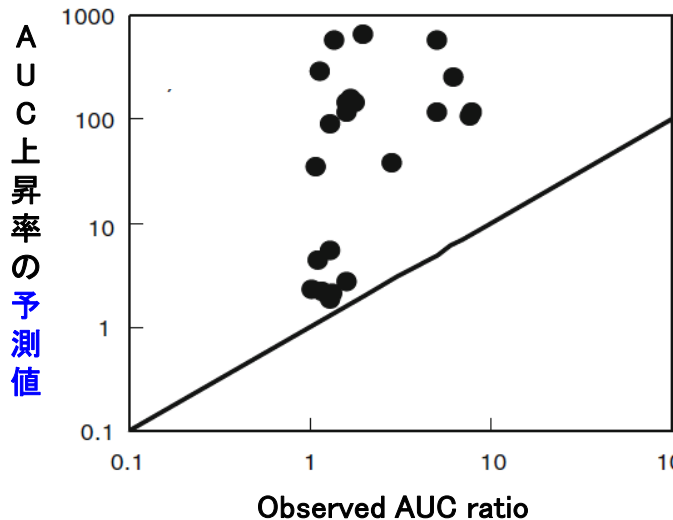


Compare DDI risks of a given compound with several known inhibitors/substrates

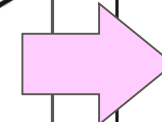
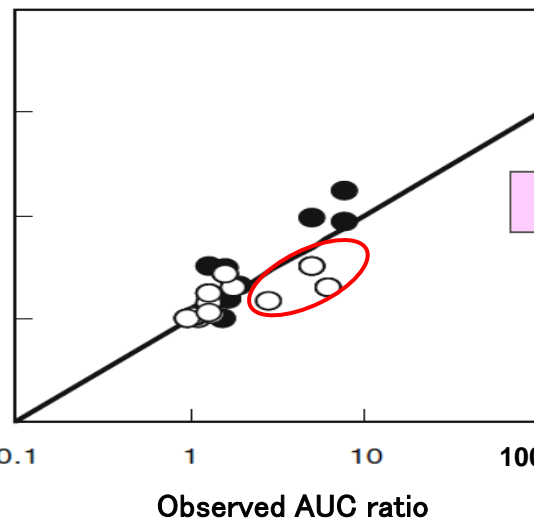
Objective

Compare simulation results with the values reported from literature

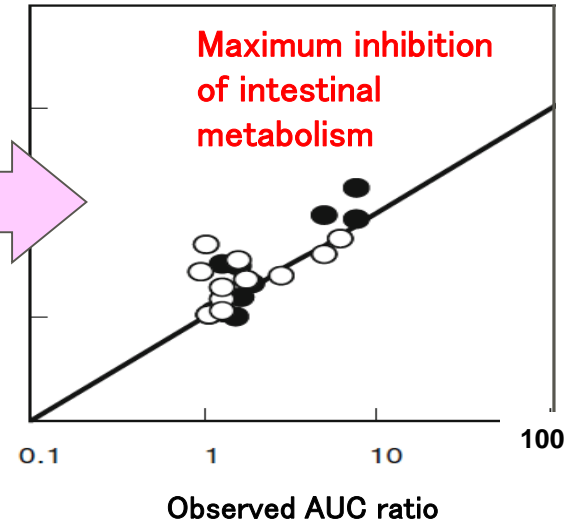
Simplified Method



PBPK Model



Maximum inhibition of intestinal metabolism



- : CYP3A4 substrates
- : non-CYP3A4 substrates

DDI Reported from Literature

Inhibitor : Itraconazole *in vitro* $K_i = 132$ ($\mu\text{g/L}$) ,
as CYP3A4 competitive inhibitor

Substrate : Triazolam as CYP3A4 substrate

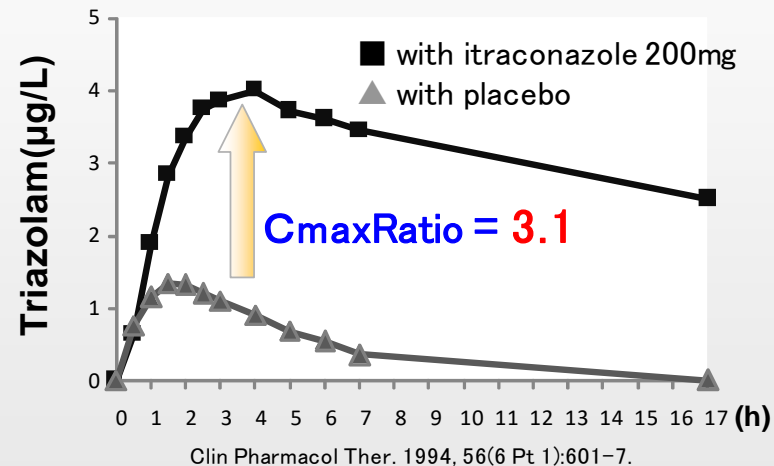
Reported literature :

DDI:

Dosing Regimen :

Itraconazole 200mg repeated 1/day for 4 days

Triazolam 0.25mg administered once on the 4th day



Confirm PK parameters in DDI Simulator

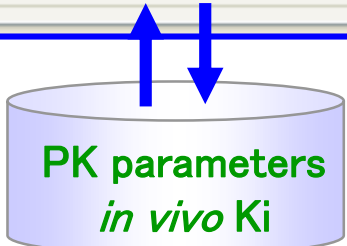
9	Glimepiride	<None>
10	Haloperidol	<None>
11	Imipramin	<None>
28	Indinavir	<None>
29	Itraconazole	<None>
30	Ketoconazole	<None>
12	Methylprednisolone	<None>
13	Metoprolol	<None>
14	Midazolam	<None>
15	Nifedipine	<None>
34	Paroxetine	<None>

Model Competitive Mechanism-Based

General Substrate Inhibitor

	Ki,vitro [µg/L]	Ki,vivo [µg/L]
1A2		
2C8		
2C9		
2C19	<i>in vitro</i> Ki	<i>in vivo</i> Ki
2D6		
3A4	132	0.282
Other		

Buttons: New, Table, Import, Delete, Groups, Export, Cancel, Save, Save As



Selecting Drug Pair for Simulation

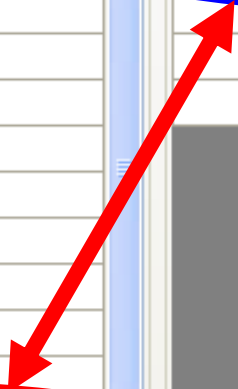
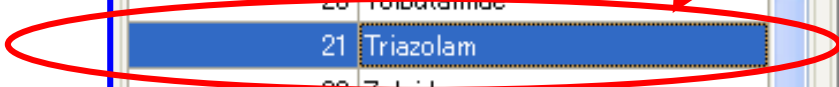
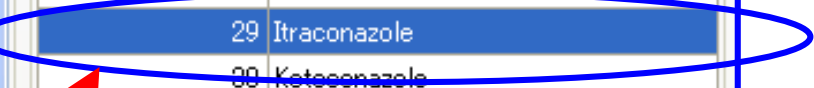
Substrate

Inhibitor

Substrates		Inhibitors	
ID	Substrate Name	ID	Inhibitor Name
7	Diazepam	23	Azithromycin
8	Fluvastatin	24	Cimetidine
9	Glimepiride	25	Fluconazole
10	Haloperidol	26	Fluoxetine
11	Imipramine	27	Fluvoxamine
12	Methylprednisolone	28	Indinavir
13	Metoprolol	29	Itraconazole
14	Midazolam	30	Ketoconazole
15	Nifedipine	31	Propafenone
34	Paroxetine	32	Quinidine
32	Quinidine		
16	Sildenafil		
17	Simvastatin		
18	Tacrolimus		
19	Tirilazad		
20	Tolbutamide		
21	Triazolam		
22	Zolpidem		

Triazolam

Itraconazole



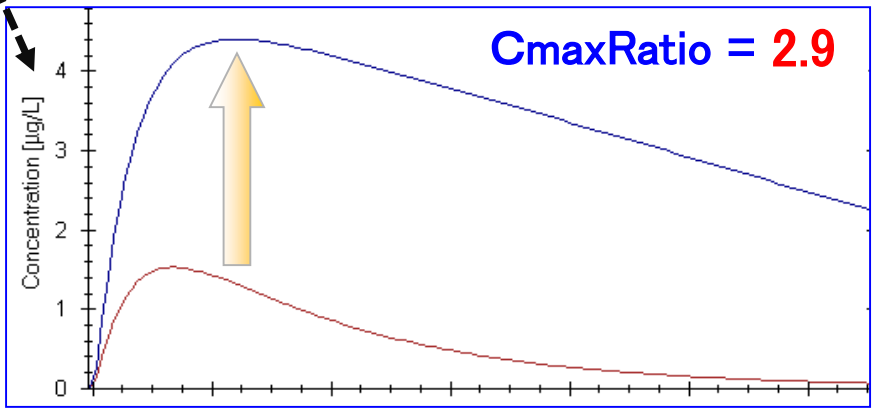
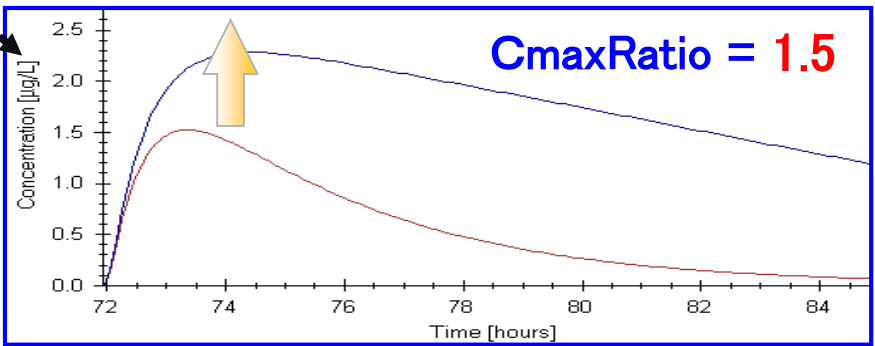
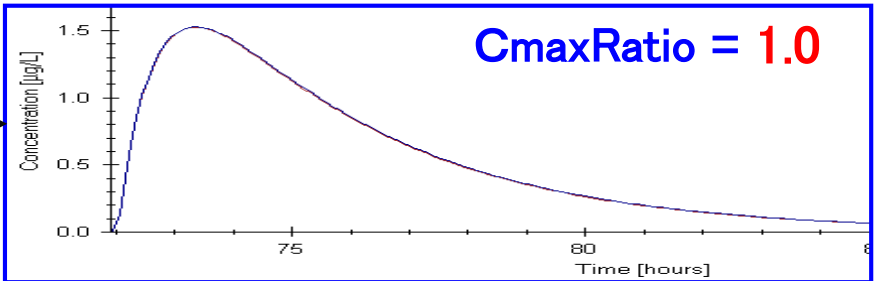
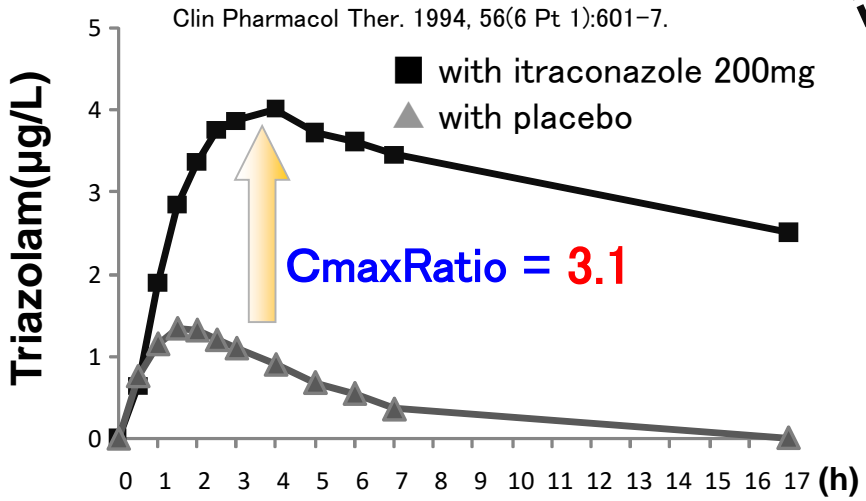
Dosing Regimen

Substrate		Inhibitor	
Triazolam		Itraconazole	
Dose [mg]	<input type="text" value="0.25"/>	Dose [mg]	<input type="text" value="200"/>
No. of times per day	<input type="text" value="1"/>	No. of times per day	<input type="text" value="1"/>
No. of days	<input type="text" value="1"/>	No. of days	<input type="text" value="4"/>
Substrate Timing		Calculate Inhibitor Steady State	
Start at	<input type="text" value="0"/> [h] after inhibitor dose number	<input type="text" value="4"/>	
Preview			

Simulation Results

Ki values used in simulation	
<i>in vitro</i> Ki	①
predicted <i>in vivo</i> Ki	②
predicted <i>in vivo</i> Ki (FaFg=1)	③

Maximum inhibition of CYP3A4
in the intestines



1-3 DDI Simulator Advantages

Item	Functionality		DDI Simulator	Simplified Method	DDI Simulator Advantages
P R E D I C T I O N	Prediction method used		PBPK	1+I/Ki	
	DDI risk criteria	AUC ratio	○	△	Less "false positive" predictions
		Cmax ratio	○	×	Verify risk due to rise in Cmax
		half-life	○	×	Verify risk due to prolonged half-life
	DDI verification	as inhibitor	○	△	Better prediction accuracy
		as substrate	○	×	Verify risk of becoming a victim drug
D B	PK parameters of well-known substrates/inhibitors (incl. <i>in vivo</i> Ki)		○		Better prediction accuracy using human <i>in vivo</i> Ki
	Customize using in-house data		○		Register in-house compound data
S I M U L A T I O N	<i>in vivo</i> Ki predicted from <i>in vitro</i> Ki		○		Better prediction for compounds w/ high logP when only <i>in vitro</i> Ki is available
	Inhibition of Intestinal Metabolism		○		Verify risk due to inhibition of intestinal metabolism
O P E R A T I O N	Dosing regimen settings		○		Minimize risk by adjusting the dosing regimen of the substrate and inhibitor
	Batch simulation of multiple drug pairs		○		Run multiple simulations at one time
	Visualize prediction results		○		Visualize the changes in plasma concentration profile

Objective

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

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) *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

Parameters calculated from experimental data

DrugX parameters calculated from experimental data and registered in DDI Simulator

Drug details

ID: 38

Name: DrugX

Common name:

Group: Demo110208

Model: Competitive Mechanism-Based

General | Substrate | Inhibitor

LogP: 2.5

FaFg: 1

fu,p: 0.3

ka [1/h]: 0.595

k12 [1/h]: 0

CLh,int [L/h]: 57.9

Clr [L/h]: 1.28

Rb: 2.4

V1 [L]: 69.1

k21 [1/h]: 0

Dose [mg]: 100

Input Data			=入力値
parameter	Value	Unit	=自動計算値
logP	2.5	-	
fu,p(human)	0.3	-	
fu,p(rat)	0.3	-	
Rb(human)	2.4	-	
Rb(rat)	2.4	-	
CLh,int(human)	57.9	L/h	
CLr(Rat)	0.03	L/h	
BW(rat)	0.25	kg	
BW(human)	70	kg	
Vb (human)	0.07	L/kg	
Vb (rat)	0.064	L/kg	
Vd(rat)	1	L/kg	
ka(rat)	0.8	h ⁻¹	
FaFg(human)	1	-	
K12	0	h ⁻¹	
K21	0	h ⁻¹	

Parameter Calculation Sheet

temporary result		
fb	0.25	-
CLh	6.7	L/h
Fh	0.93	-
Vd(human)	70.42	L
P	316.23	-
fu,p/fu,t	0.7	-
Kp,h	2.34	-

Output					
DDI Simulator Parameter					
Parameter	Value	unit	Parameter	Value	unit
logP	2.50	-	CLr	1.28	L/h
FaFg	1.0	-	Rb	2.4	-
fu,p	0.3	-	V1	69.1	L
ka	0.595	h ⁻¹	k21	0	h ⁻¹
k12	0	h ⁻¹	Dose	100	mg
CLh,int	57.9	L/h			

Experimental Data Input

Automatically Calculated Parameters

Single Dose Simulation (Competitive Inhibition Model)

Substrate / Inhibitor Selection

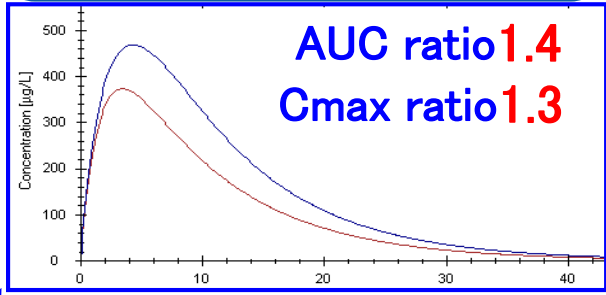
Substrate		Inhibitor	
2	Atorvastatin	23	Azithromycin
5	Desipramine	24	Cimetidine
6	Dexamethasone	25	Fluconazole
7	Diazepam	26	Fluoxetine
38	DrugX	27	Fluvoxamine
8	Fluvastatin	28	Indinavir
9	Glimepiride	29	Itraconazole
10	Haloperidol	30	Ketoconazole
		31	Propafenone
		32	Quinidine

DrugX and Ketoconazole pair

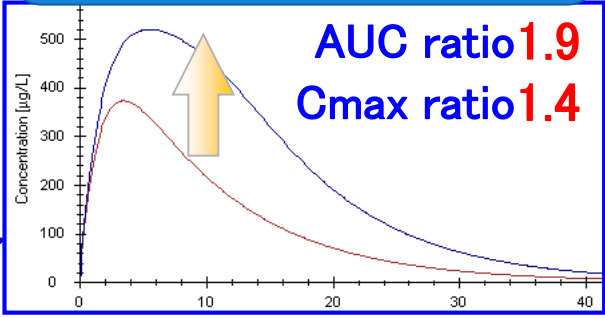
Dosing Regimen

DrugX				Ketoconazole			
Dose [mg]	<input type="text" value="100"/>	No. of times per day	<input type="text" value="1"/>	Dose [mg]	<input type="text" value="200"/>	No. of times per day	<input type="text" value="1"/>
		No. of days	<input type="text" value="1"/>			No. of days	<input type="text" value="1"/>

Results (in vitro Ki)



Results (in vivo Ki)



2-1 Demonstration 1 (Substrate)

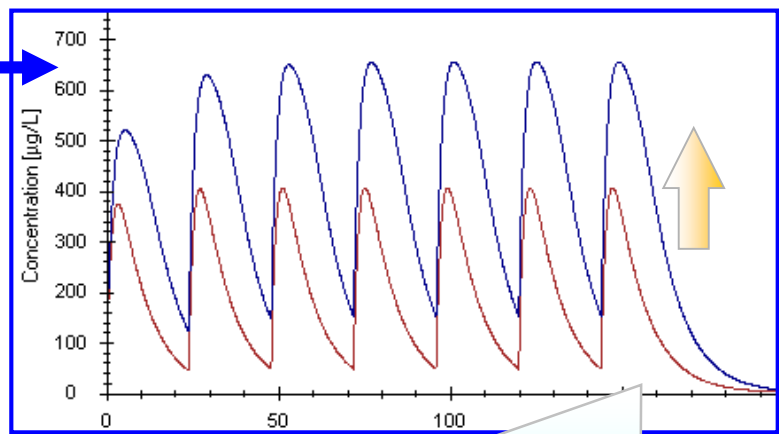
Repeated Dose Simulation (Competitive Inhibition Model)

Dosing Regimen

Substrate		Inhibitor	
DrugX	Ketoconazole		
Dose [mg] <input type="text" value="100"/>	Dose [mg] <input type="text" value="200"/>		
No. of times per day <input type="text" value="1"/>	No. of times per day <input type="text" value="1"/>	No. of days <input type="text" value="7"/>	No. of days <input type="text" value="7"/>
Substrate Timing <input type="text" value="7"/>		<input type="text" value="7"/>	
Start at <input type="text" value="0"/> [h] after inhibitor dose number <input type="text" value="1"/>	<input type="button" value="Calculate Inhibitor Steady State"/>		
Preview			

Results (*in vivo* Ki)

AUC ratio 1.9 → 2.1
Cmax ratio 1.4 → 1.6



Higher risk of DDI compared to single dose

Objective

Investigate the possibility of DrugY as MBI after observing an increase in its inhibitory effect due to preincubation.

Conditions

- (1) DrugY as a CYP2D6 substrate also irreversibly inhibits CYP2D6 (DrugY' s effective blood concentration is assumed to be **30**μg/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	$CL_r = 0.728 \text{ L/h}$
volume of distribution	$V_d = 1067 \text{ L/kg}$
plasma unbound fraction	$f_{u,p} = 0.05$
blood-plasma conc. ratio	$R_b = 1.0$
absorption rate constant	$k_a = 0.987 \text{ (h}^{-1}\text{)}$
hepatic intrinsic clearance	$CL_{h,int} = 3773 \text{ } \mu\text{g/L}$

(2) *in vitro* data

fraction of 2D6 metabolism	$f_{m,2D6} = 0.86$
apparent inhibition constant	$K_{i,app} = 118.07 \text{ } \mu\text{g/L}$
max. inactivation rate constant	$K_{inact} = 10.2 \text{ (h}^{-1}\text{)}$

(3) Metoprolol dosing regimen

Twice a day (1 week) Dose = 60mg

Parameter registration

DrugY parameters
to be registered
in DDI Simulator



-Drug details-

ID: 39
Name: DrugY
Model: Competitive Mechanism-Based

General | Substrate | Inhibitor

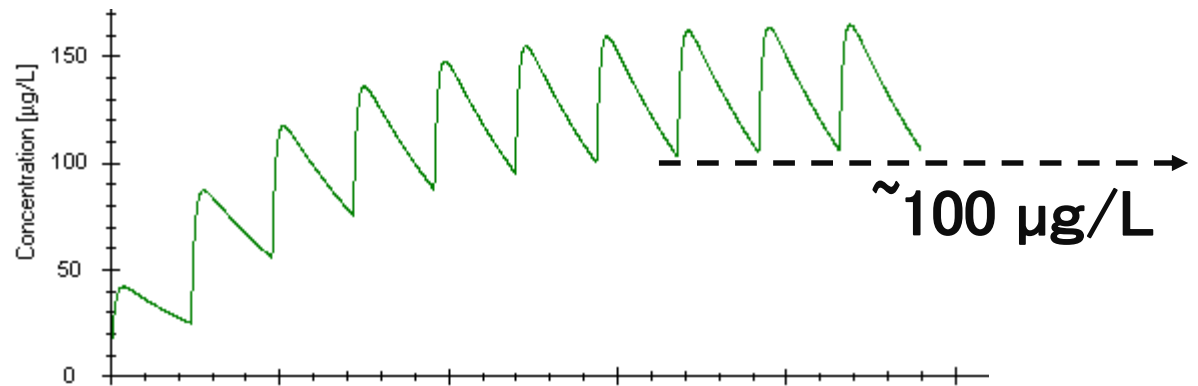
LogP	4.238	CLr [L/h]	0.728
FaFe	1	Rb	1
fup	0.05	V1 [L]	1067
ka [1/h]	0.987	k21 [1/h]	0
k12 [1/h]	0	Dose [mg]	40
CLH,int [L/h]	3773		

	fm	kinact [1/h]	Ki,app [µg/L]
1A2			
2C8			
2C9			
2C19			
2D6	0.86	10.2	118.07
3A4			
Other			

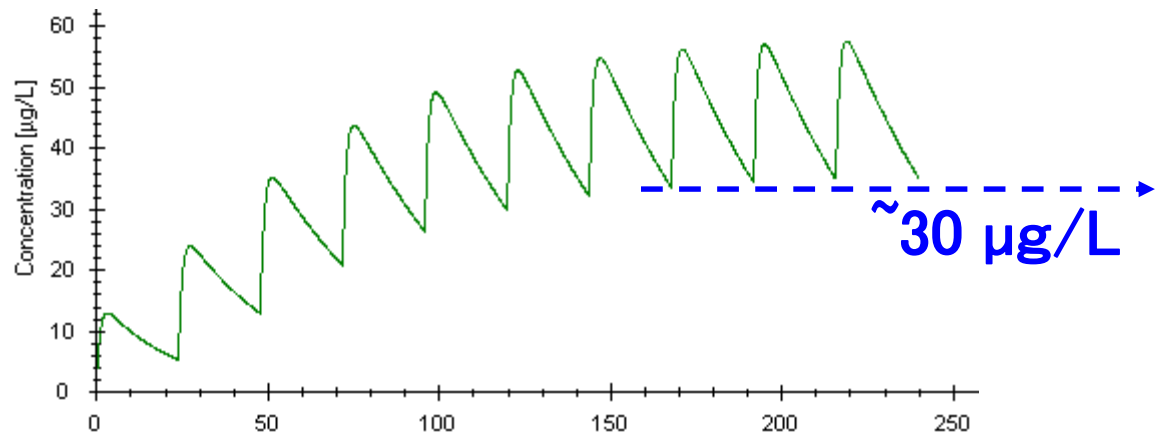
Optimized dosing regimen

Investigation of correct oral dose for DrugY in order to reach its effective blood concentration = $30\mu\text{g/L}$

100mg/day
repeated
for 10 days →



40mg /day
repeated
for 10 days →



Steady-state Calculations

Metoprolol

Dose [mg]

60

No. of times per day

2

No. of days

7

DrugY

Dose [mg]

40

No. of times per day

1

No. of days

13

Substrate Timing

Start at

0

[h]

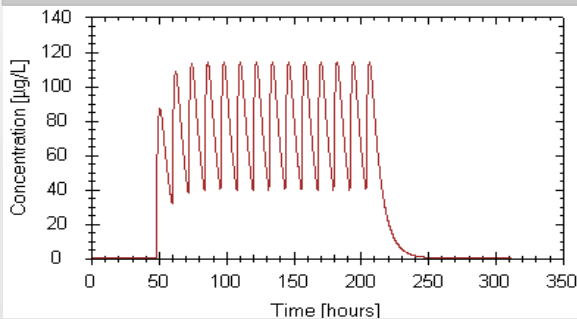
after inhibitor dose number

3

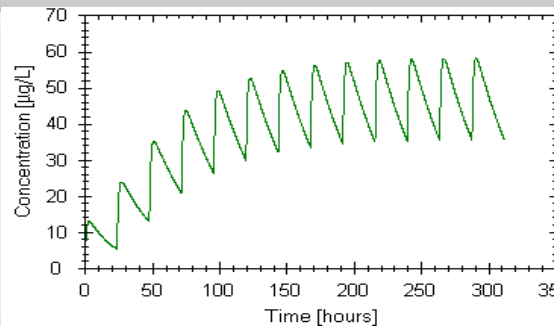


Calculate Inhibitor Steady State

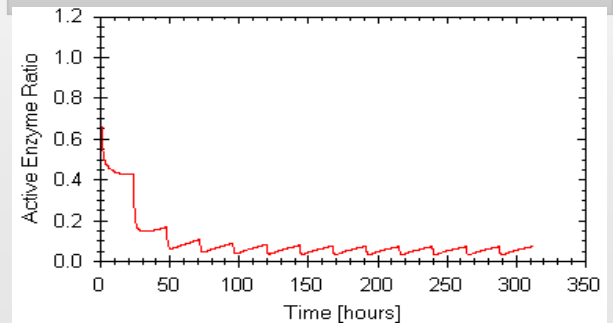
Metoprolol (Substrate)



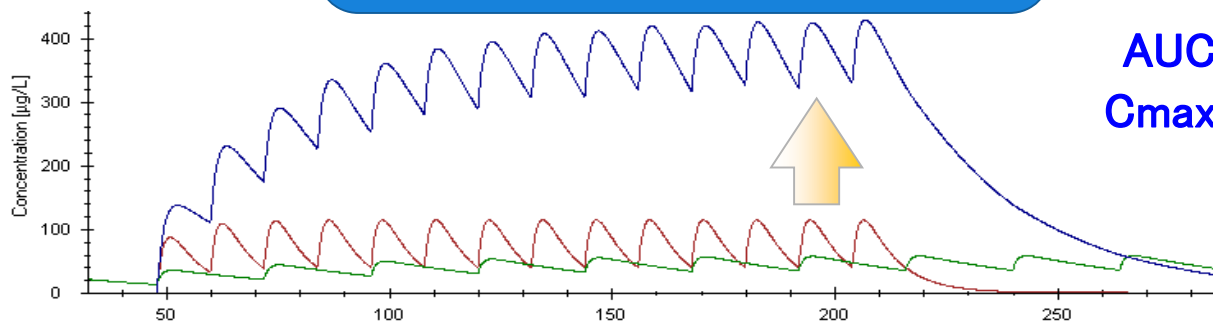
DrugY (Inhibitor)



Ratio of Active Enzymes (REact)



Predicted Results

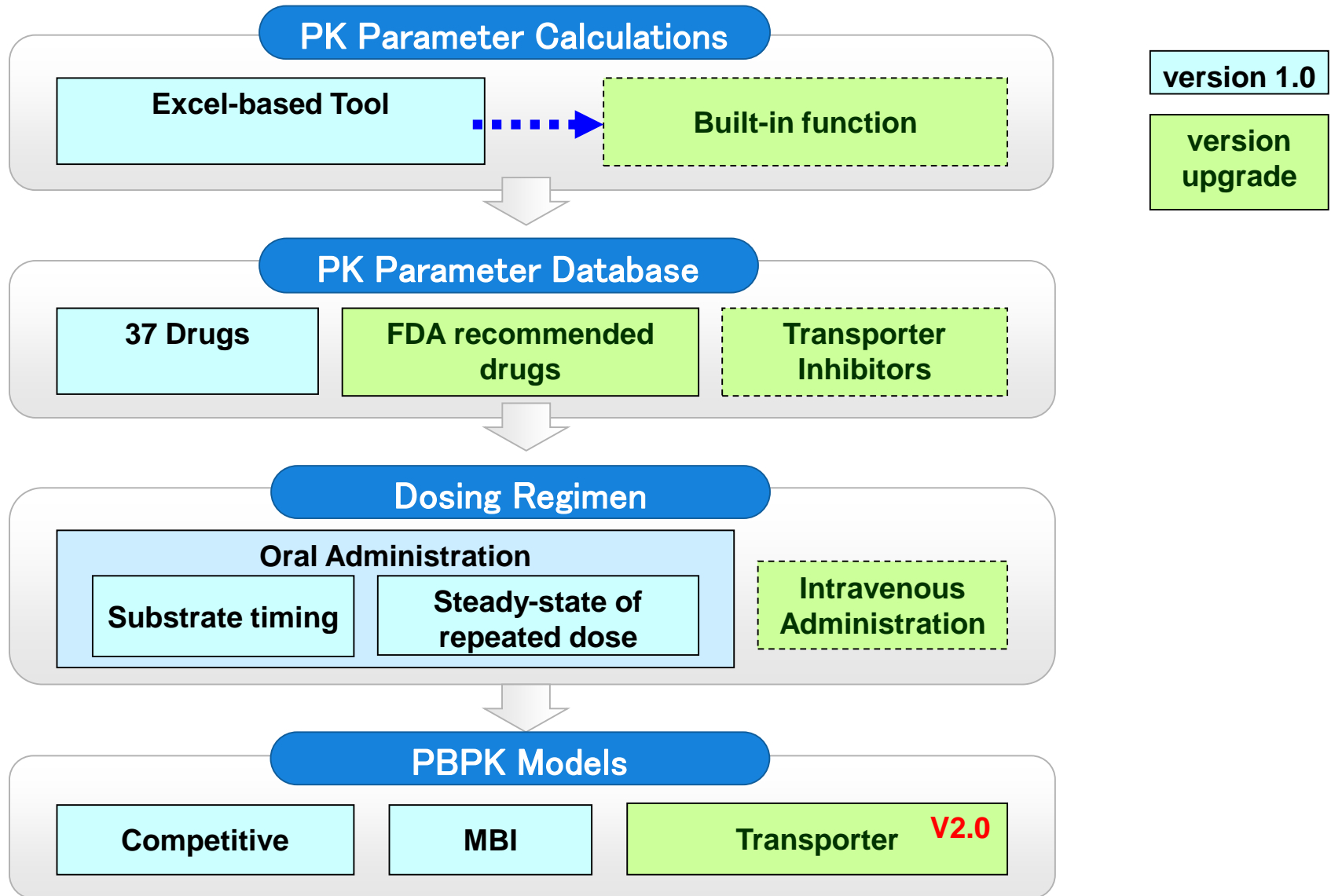


AUC ratio **4.8**
Cmax ratio **3.8**

DDI Simulator Future Enhancements

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

3. Future Plans





3. Future Plans (New Drug Data)

List of FDA recommended drugs for study of interactions

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

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


Drugs marked in black : already included in DDI Simulator
Drugs marked in red : ready for next release



FUJITSU

shaping tomorrow with you