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Introduction to DDI Simulator

Demonstration of DDI Simulator

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Contents

1-1 Main Features

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

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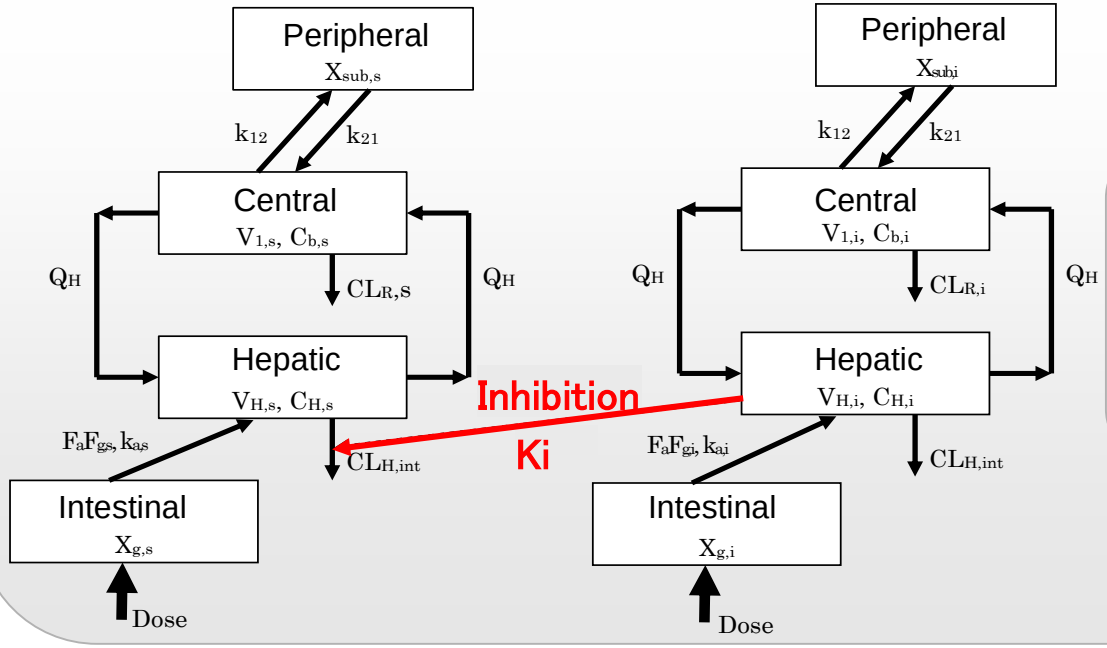
Physiologically-based Pharmacokinetic(PBPK) Model



Types of Inhibition

(1)Competitive

[Ki]

(2)Mechanism-based (MBI)

[Ki,app, kinact]

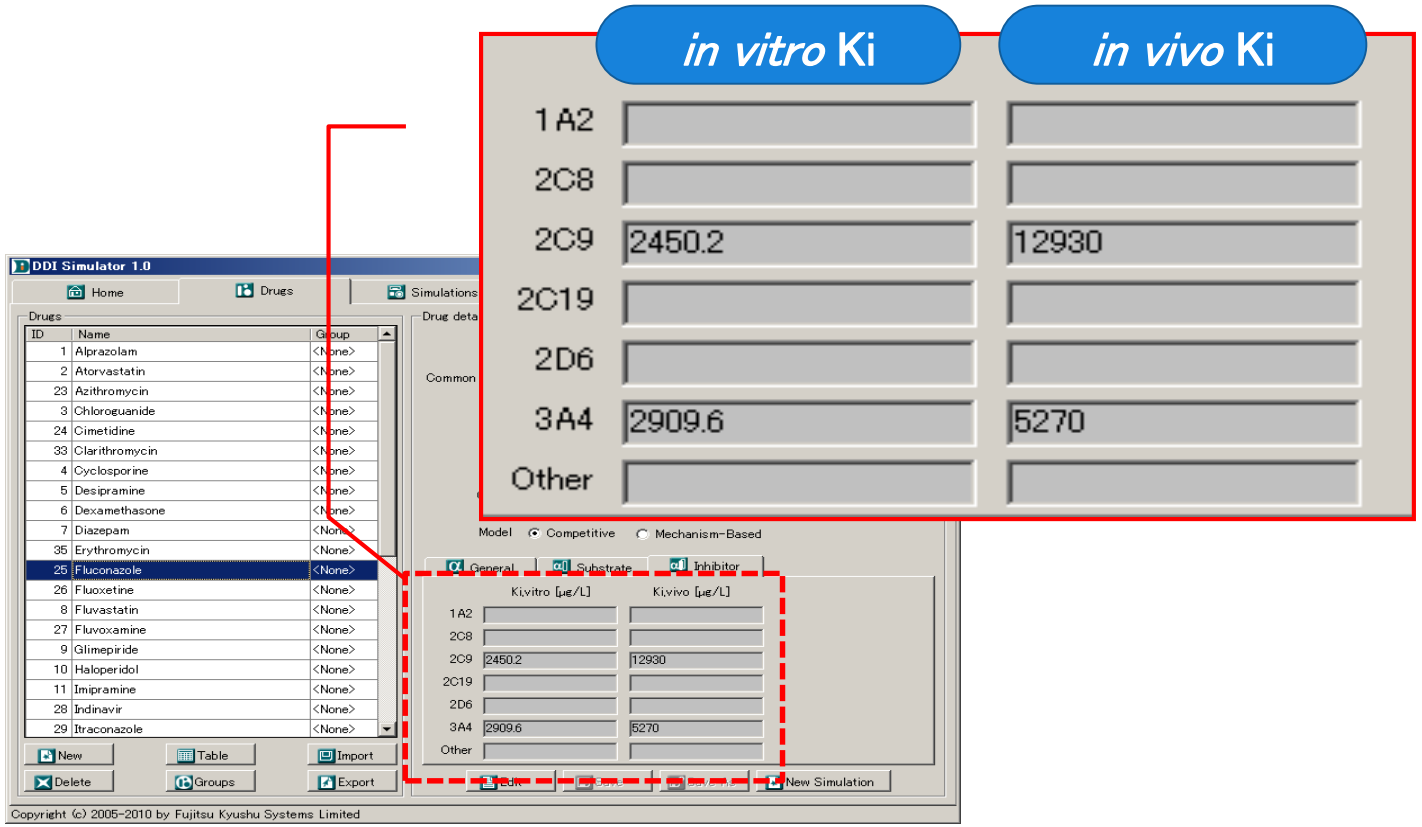
Advantages of using PBPK model

- ☑ 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

Kato M, Shitara Y, Sato H, Yoshisue K, Hirano M, Ikeda T, Sugiyama Y. Pharm Res. 2008 Aug;25(8):1891-901.

(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

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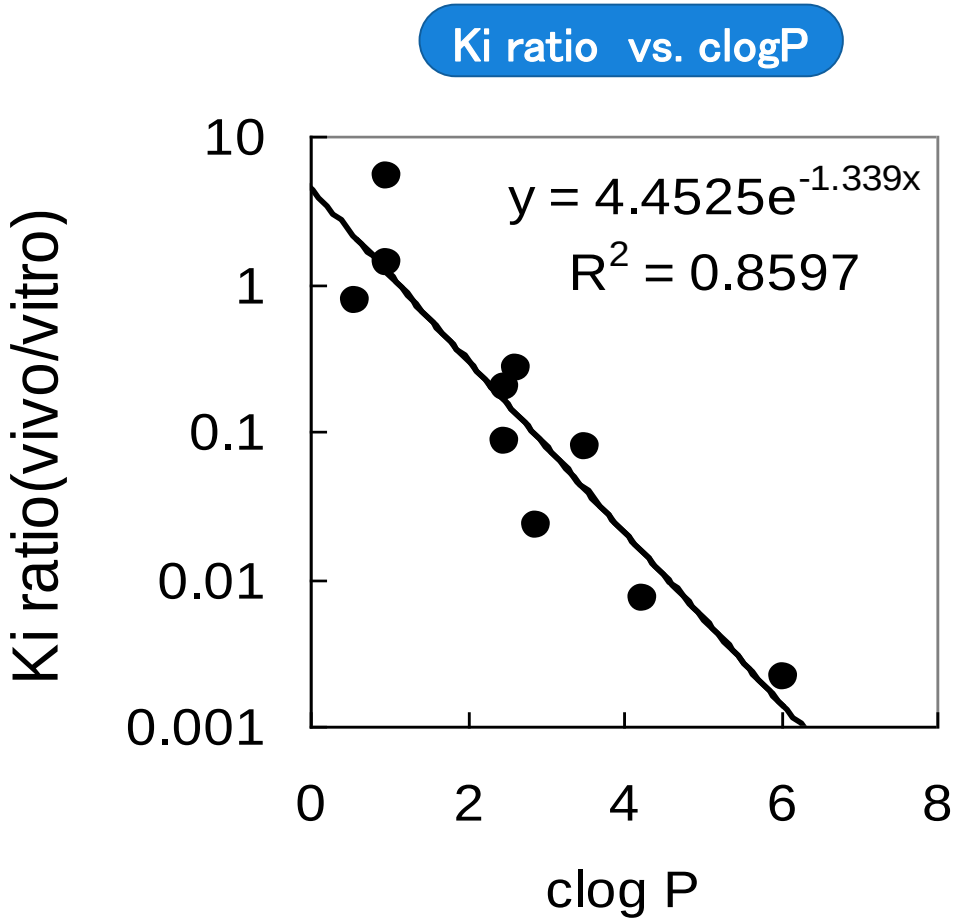
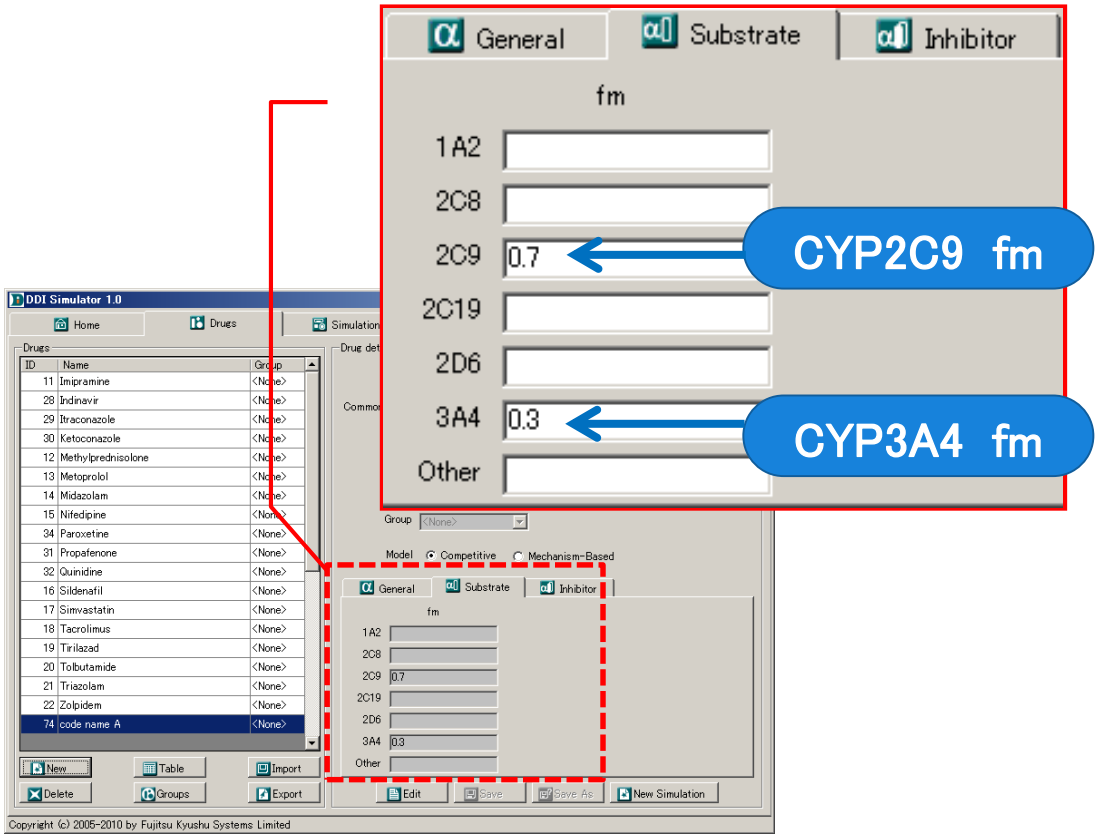
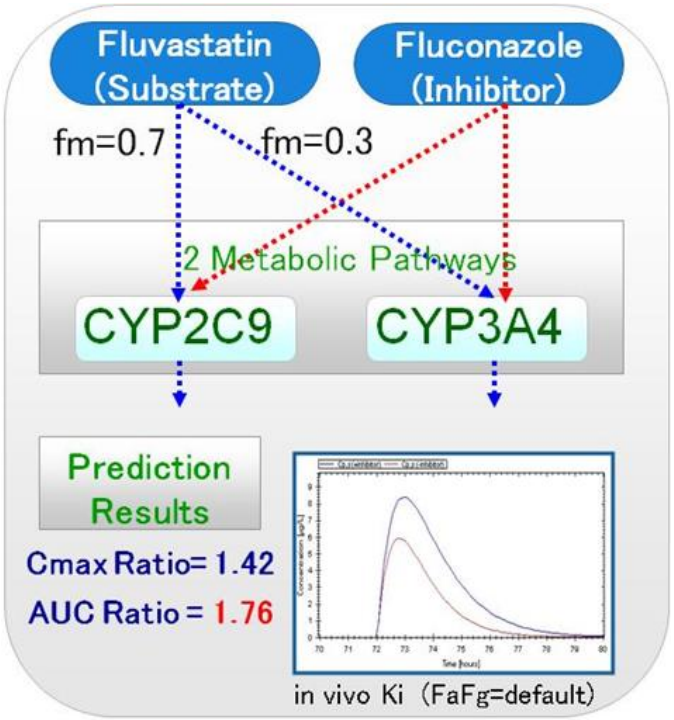
***In vivo* Ki values are automatically estimated from *in vitro* Ki using the Ki ratio and clogP relationship shown below**



(4) Inhibition of Multiple CYP Isoforms

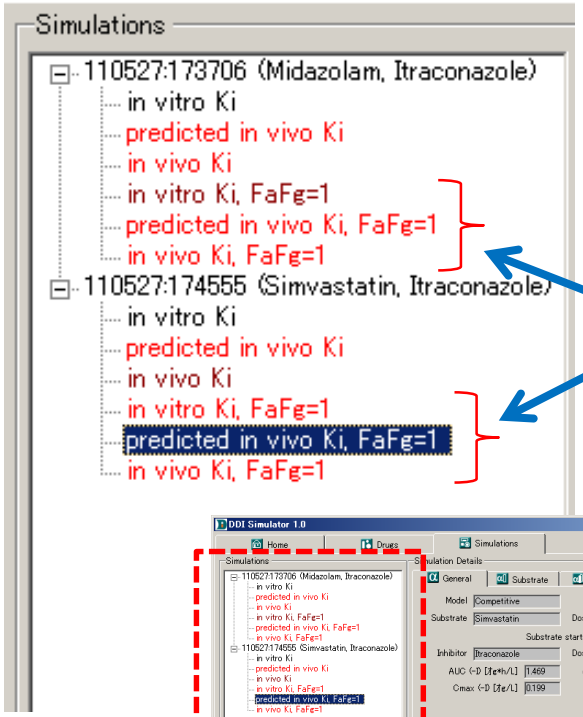
Only CYP isoforms with fm (fraction of metabolism) values assigned are subject to inhibition



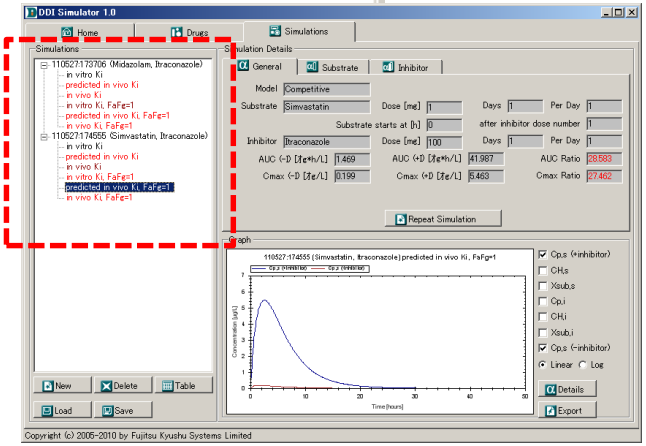


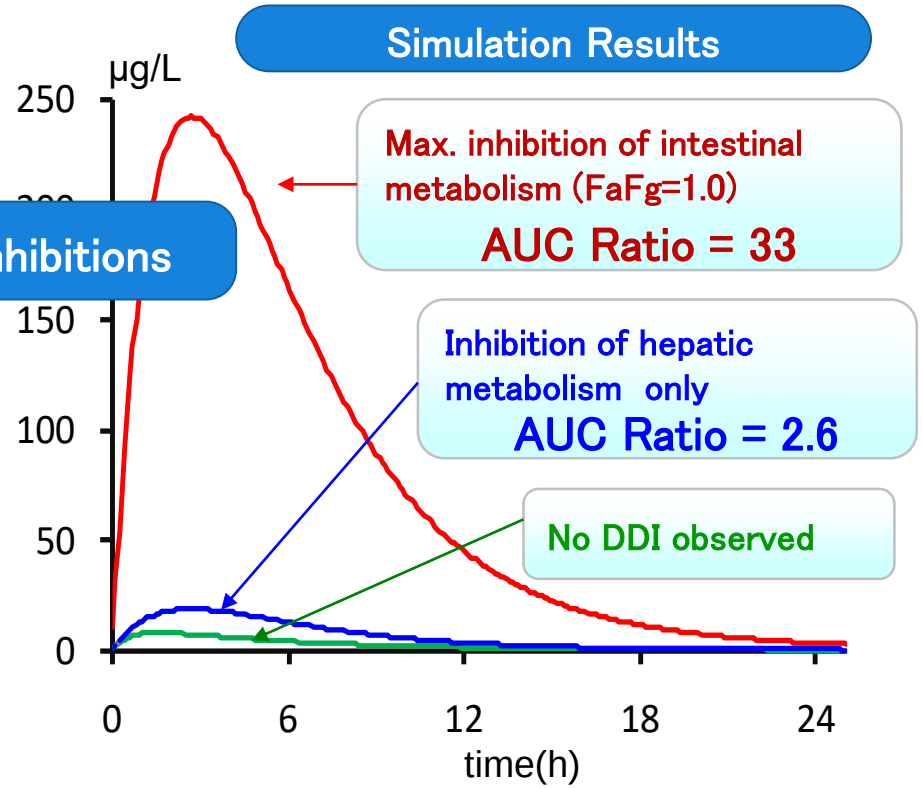
(5) Inhibition of Intestinal Metabolism

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

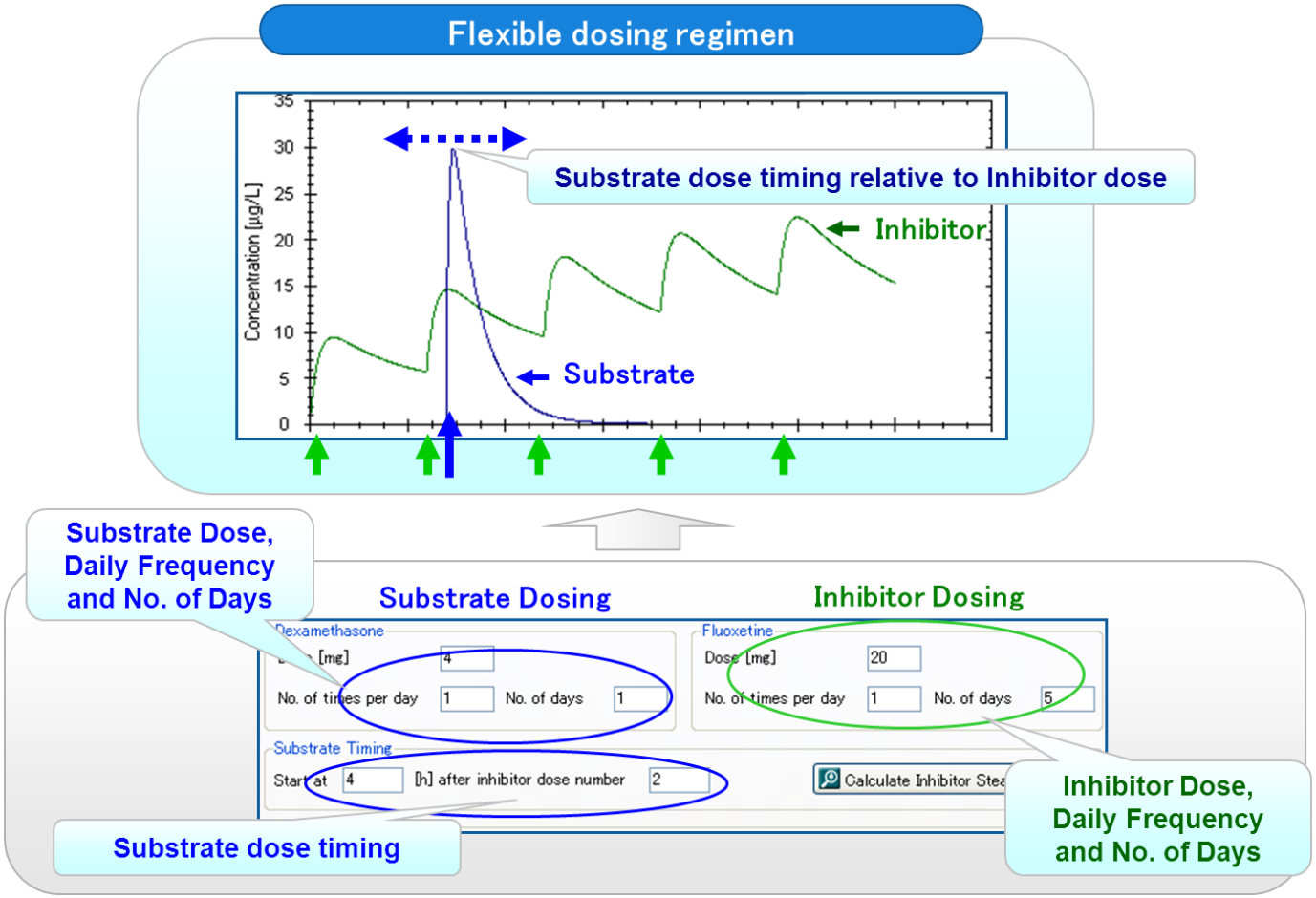


maximum inhibitions



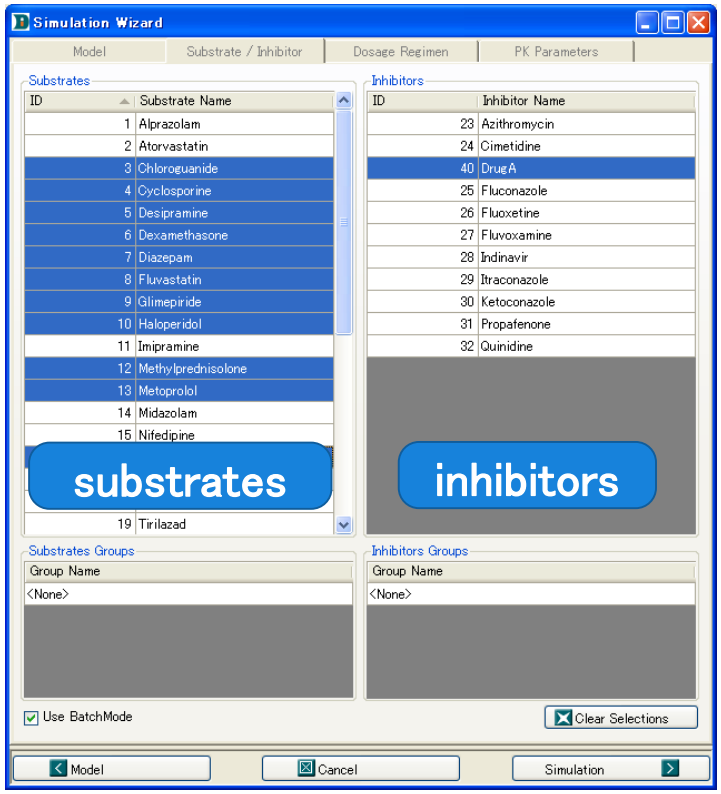


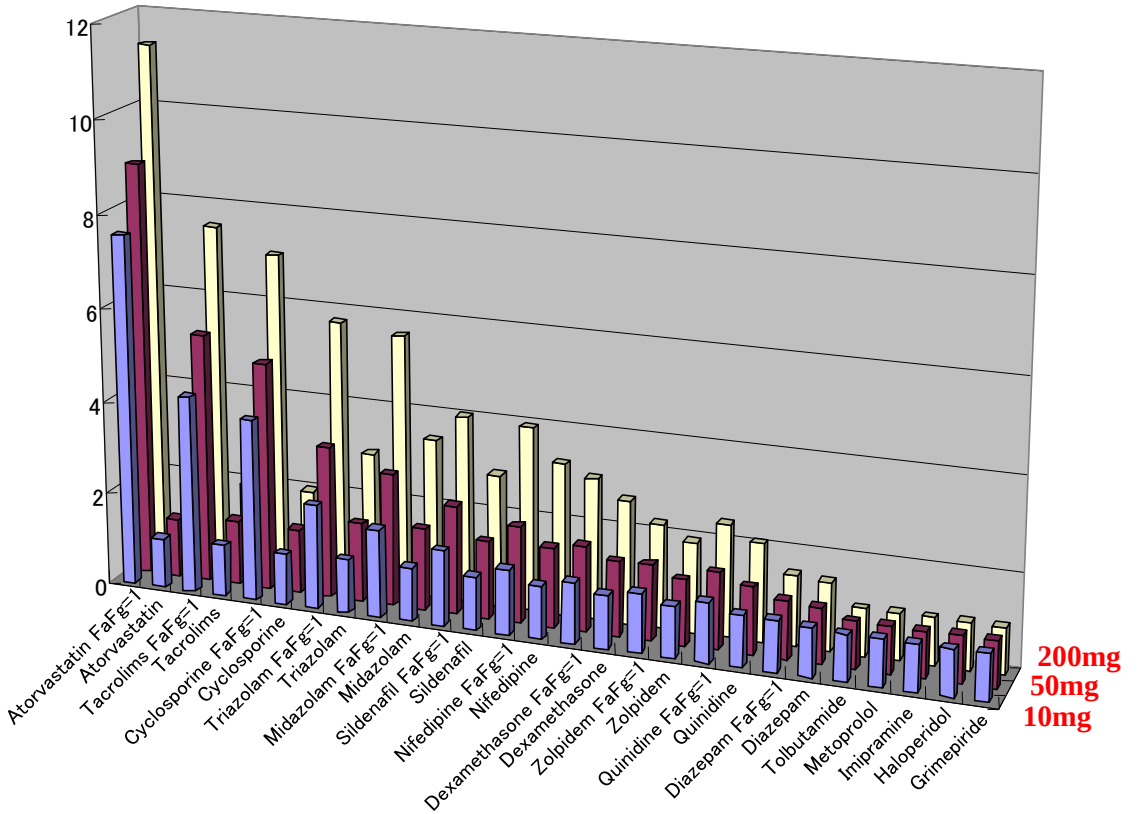
(6) Dosing Regimen Optimization



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

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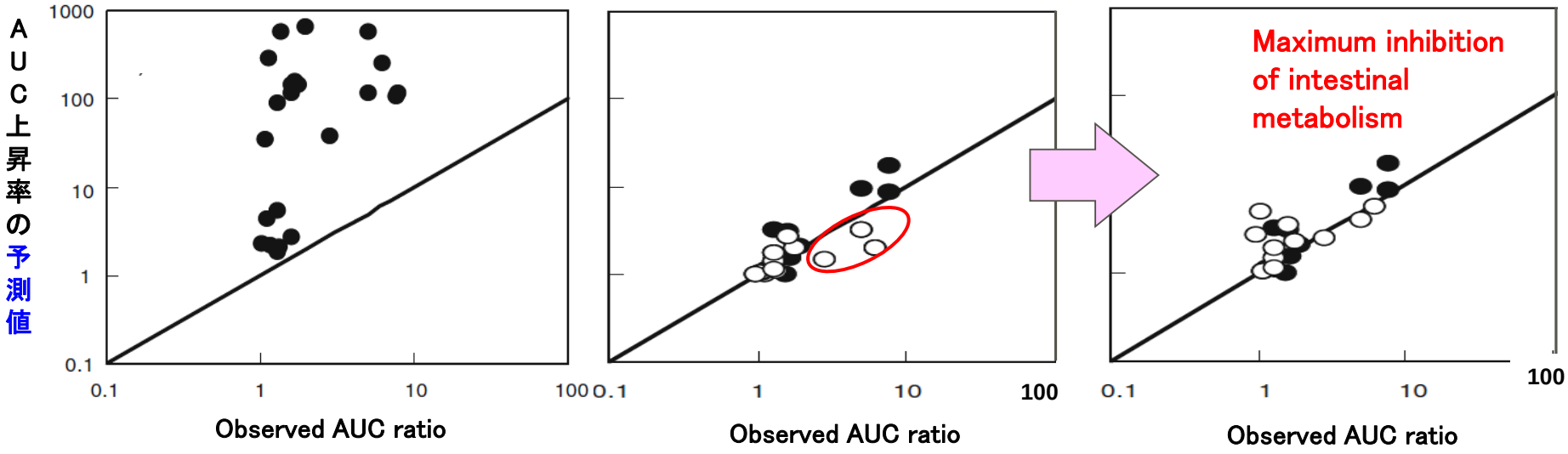
Objective

Compare simulation results with the values reported from literature

Simplified Method

PBPK Model



○ : CYP3A4 substrates

● : non-CYP3A4 substrates

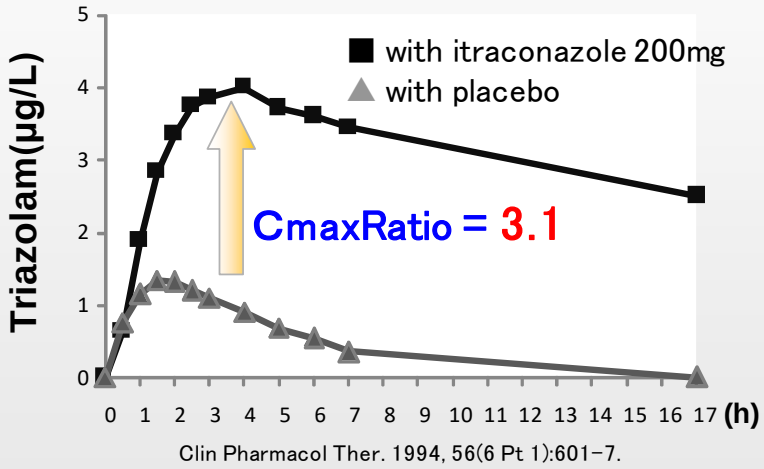
DDI Reported from Literature

Inhibitor : Itraconazole *in vitro* Ki = 132 (μg/L) ,
as CYP3A4 competitive inhibitor

Substrate : Triazolam as CYP3A4 substrate

Reported literature :

DDI :



Clin Pharmacol Ther. 1994, 56(6 Pt 1):601-7.

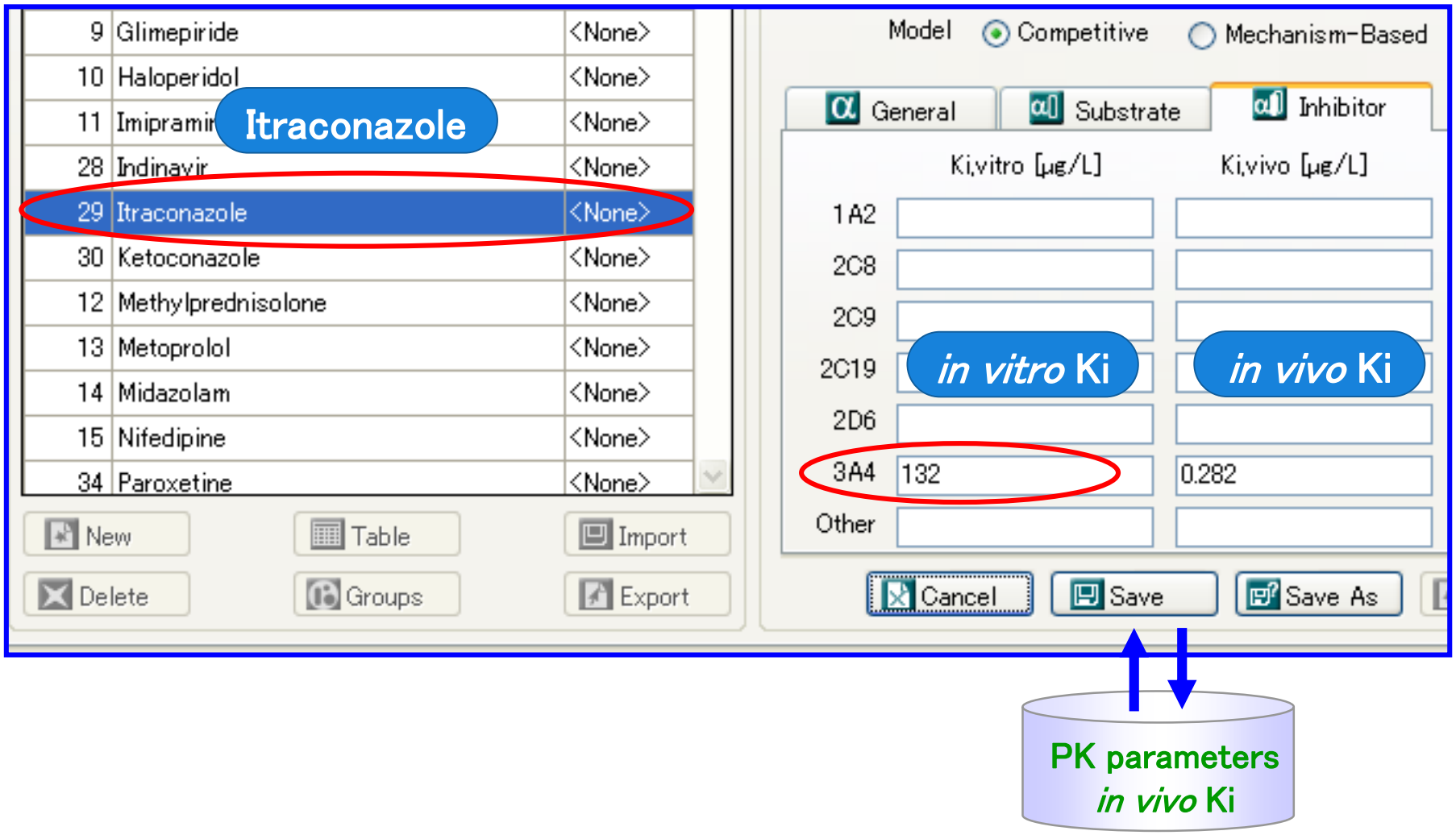
Dosing Regimen :

Itraconazole 200mg repeated 1/day for 4 days

Triazolam 0.25mg administered once on the 4th day

1-2 Validity of Results

Confirm PK parameters in DDI Simulator



1-2 Validity of Results

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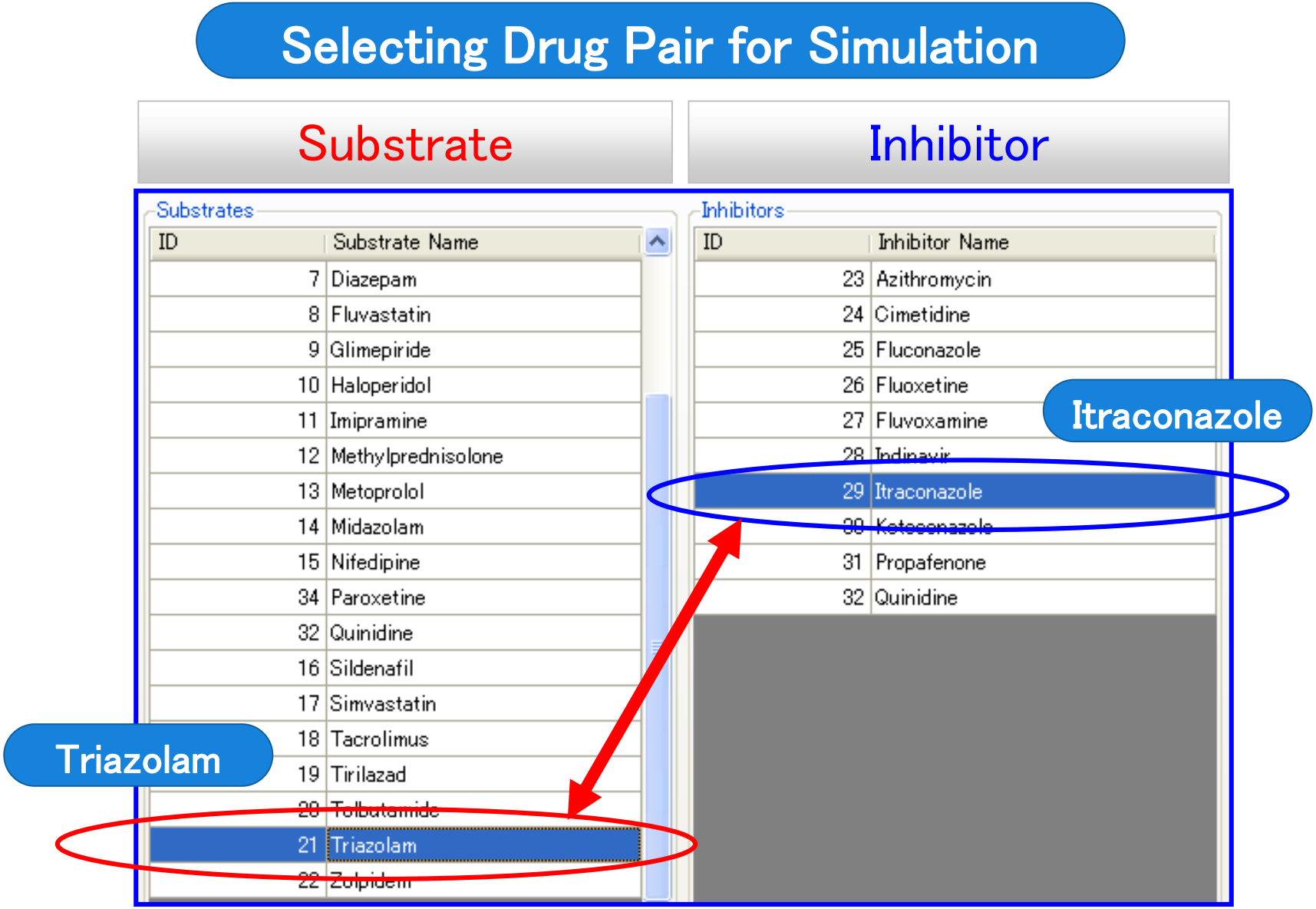
Selecting Drug Pair for Simulation



1-2 Validity of Results

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Dosing Regimen

Substrate	Inhibitor

Triazolam

Dose [mg] 0.25

No. of times per day 1 No. of days 1

Itraconazole

Dose [mg] 200

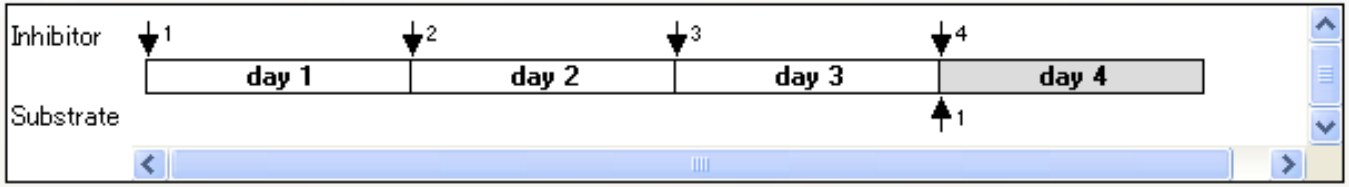
No. of times per day 1 No. of days 4

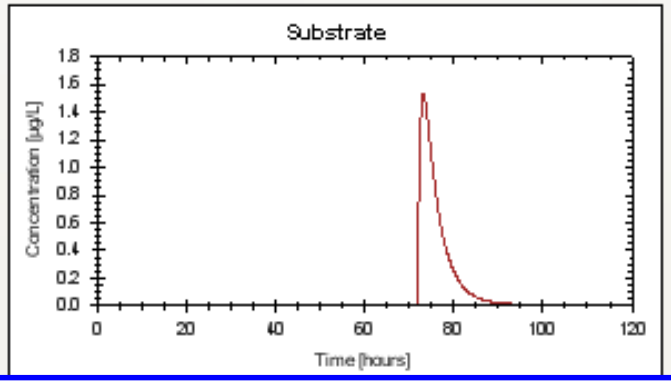
Substrate Timing

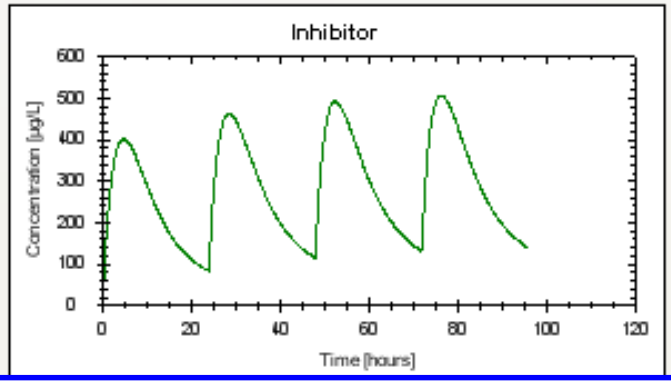
Start at 0 [h] after inhibitor dose numbe 4

Calculate Inhibitor Steady State

Preview







1-2 Validity of Results

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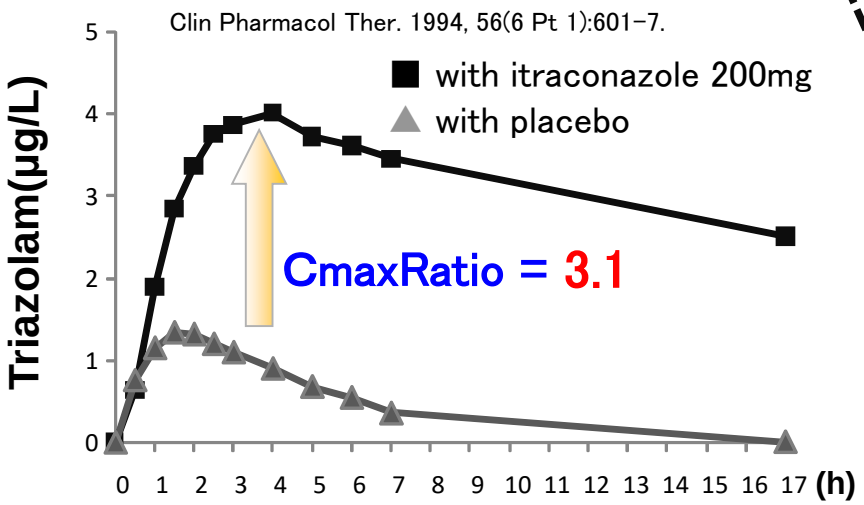
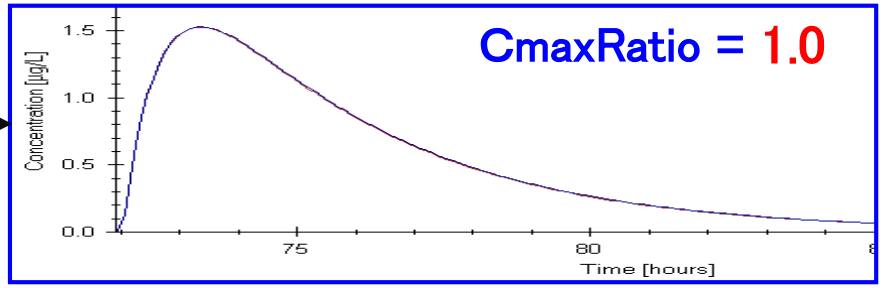
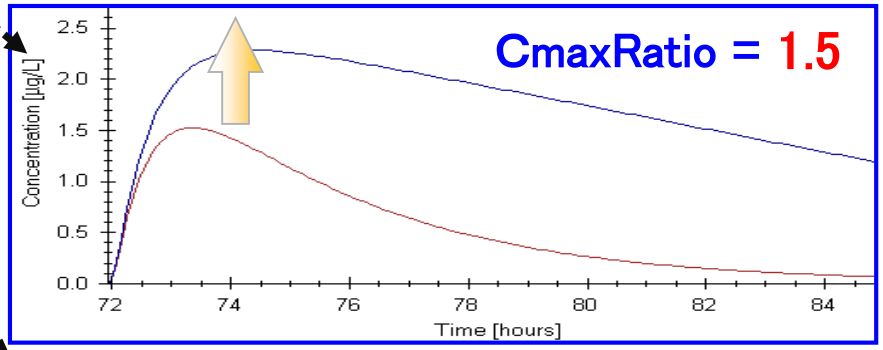
Simulation Results

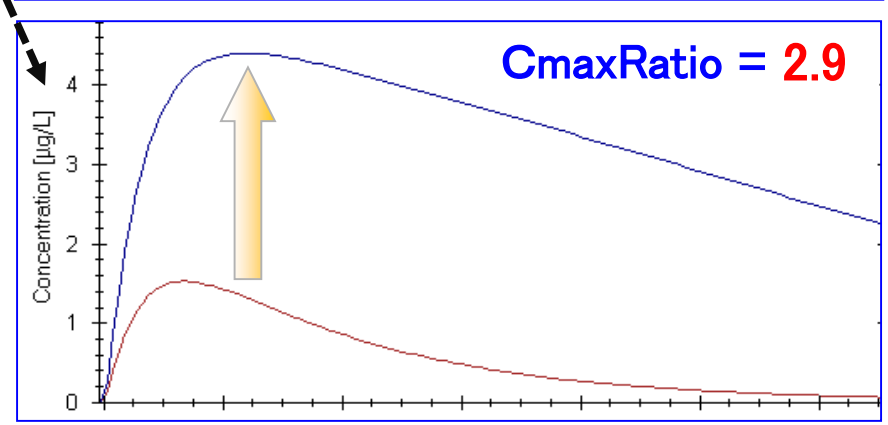
Ki values used in simulation	
in vitro Ki	①
predicted *in vivo* Ki	②
predicted *in vivo* Ki (FaFg=1)	③

Maximum inhibition of CYP3A4 in the intestines









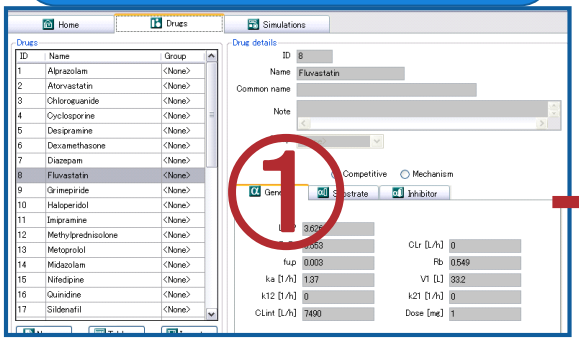
1-3 DDI Simulator Advantages

Item	Functionality		DDI Simulator	Simplified Method	DDI Simulator Advantages
PREDICTION	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
DB	PK parameters of well-known substrates/inhibitors (incl. *in vivo* Ki)		○		Better prediction accuracy using human *in vivo Ki*
	Customize using in-house data		○		Register in-house compound data
EXTENSION	*in vivo* Ki predicted from *in vitro* Ki		○		Better prediction for compounds w/ high logP when only *in vitro* Ki is available
	Inhibition of Intestinal Metabolism		○		Verify risk due to inhibition of intestinal metabolism
OPERATION	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

2. Demonstration

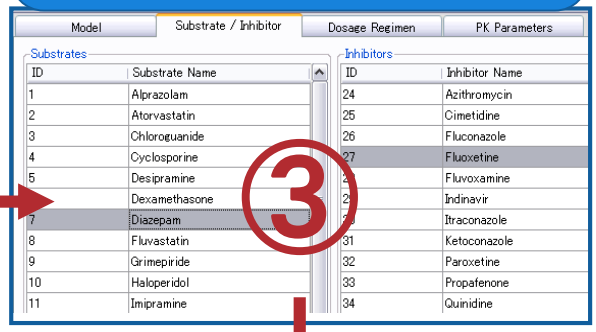
Basic Flow of Simulations

Add/Edit Drug PK data



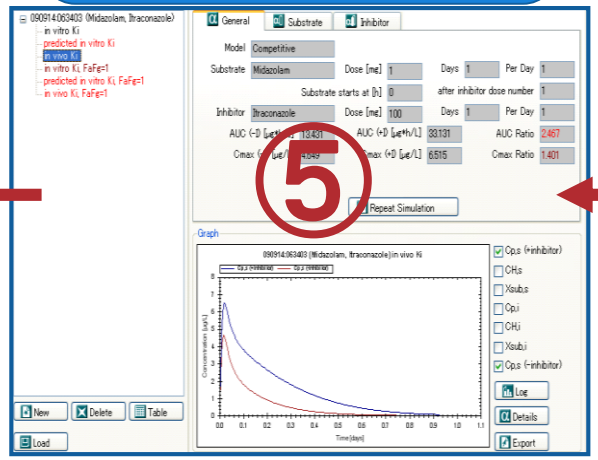
Choose a Simulation Model

Select Substrate/Inhibitor

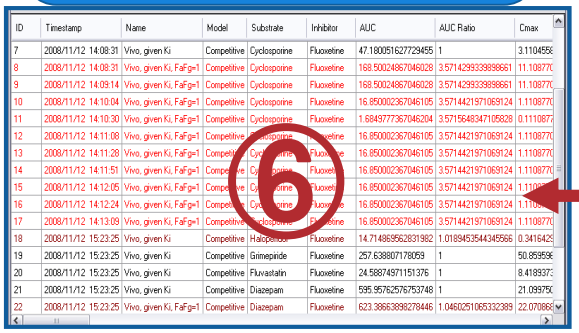


Set Dosing Regimen

Run Simulations



Confirm Results



2-1 Demonstration 1 (Substrate)

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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)

2-1 Demonstration 1 (Substrate)

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Known experimental data

(1) Rat data

octanol-water partition coef.	logP = 2.5
plasma unbound fraction	fu,p = 0.3
blood-plasma conc. ratio	Rb = 2.4
renal clearance	CLr = 0.03 L/h
volume of distribution	Vd = 1.0 L/kg
absorption rate constant	ka = 0.8 (h^{-1})

(2) *in vitro* data

metabolised by CYP3A4 only	$fm_{,3A4}$ = 1.0
hepatic intrinsic clearance	CLh,int = 57.9 L/h

(3) Ketoconazole dosing regimen

Once a day Dose = 200mg

2-1 Demonstration 1 (Substrate)

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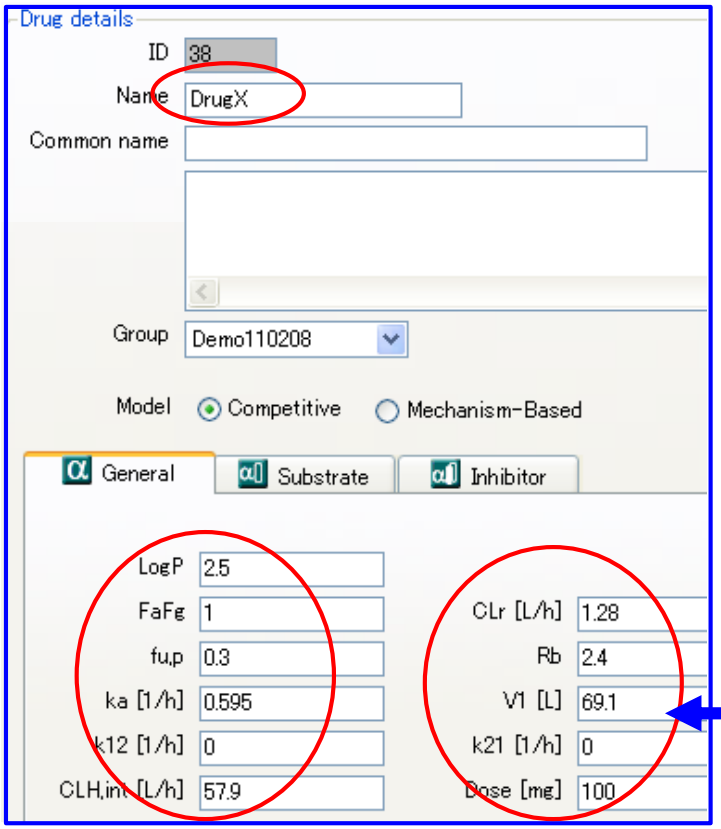
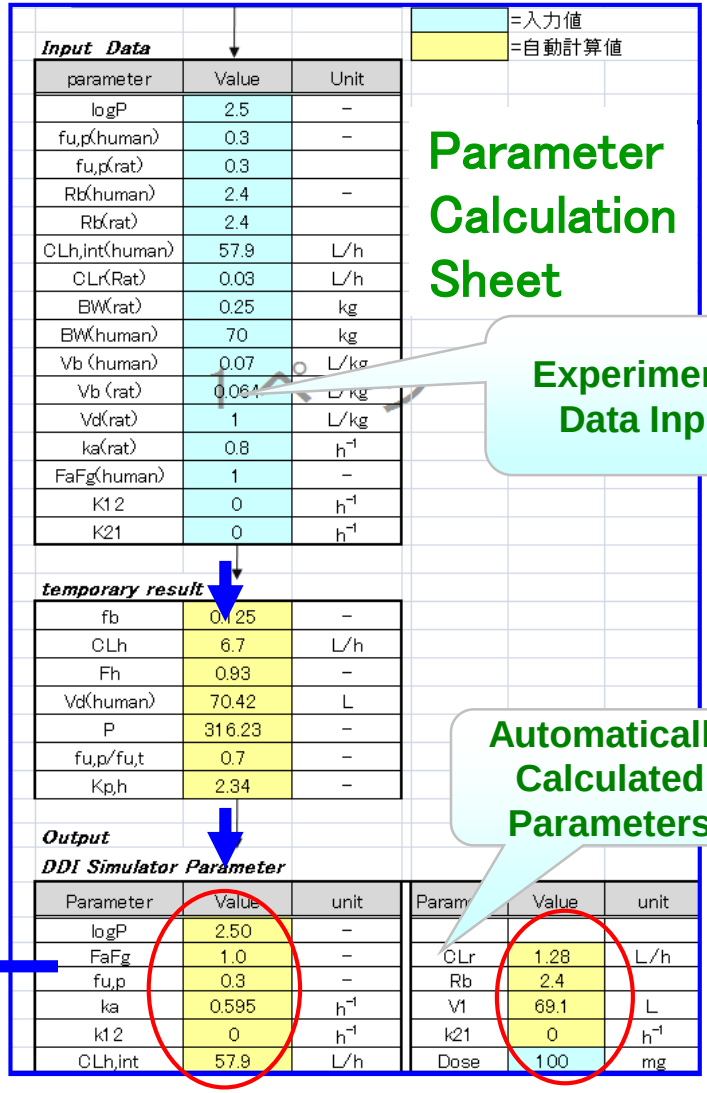
Parameters calculated from experimental data

DrugX parameters calculated from experimental data and registered in DDI Simulator





2-1 Demonstration 1 (Substrate)

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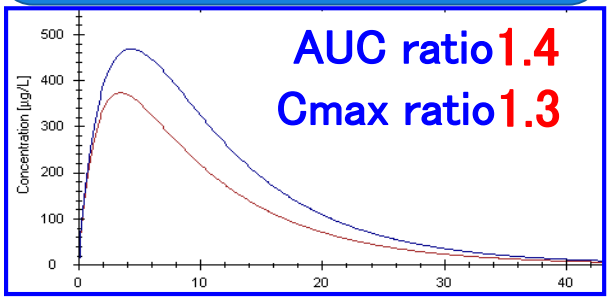
Single Dose Simulation (Competitive Inhibition Model)

Substrate / Inhibitor Selection

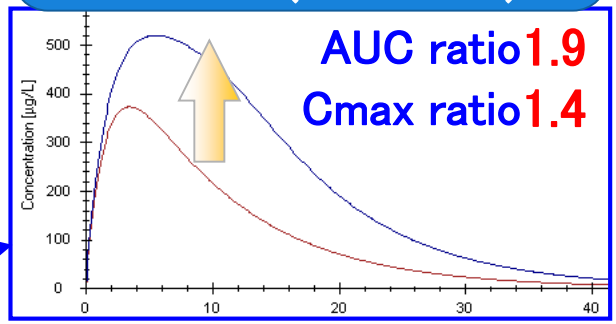
Substrate		Inhibitor	
2	Atorvastatin	23	Azithromycin
		24	Cimetidine
		25	Fluconazole
5	Desipramine	26	Fluoxetine
6	Dexamethasone	27	Fluvoxamine
7	Diazepam	28	Indinavir
38	DrugX	29	Itraconazole
8	Fluvastatin	30	Ketoconazole
9	Glimepiride	31	Propafenone
10	Haloperidol	32	Quinidine

DrugX and Ketoconazole pair

Results (*in vitro* Ki)



Results (*in vivo* Ki)



Dosing Regimen

DrugX			Ketoconazole		
Dose [mg]	100		Dose [mg]	200	
No. of times per day	1	No. of days 1	No. of times per day	1	No. of days 1

2-1 Demonstration 1 (Substrate)

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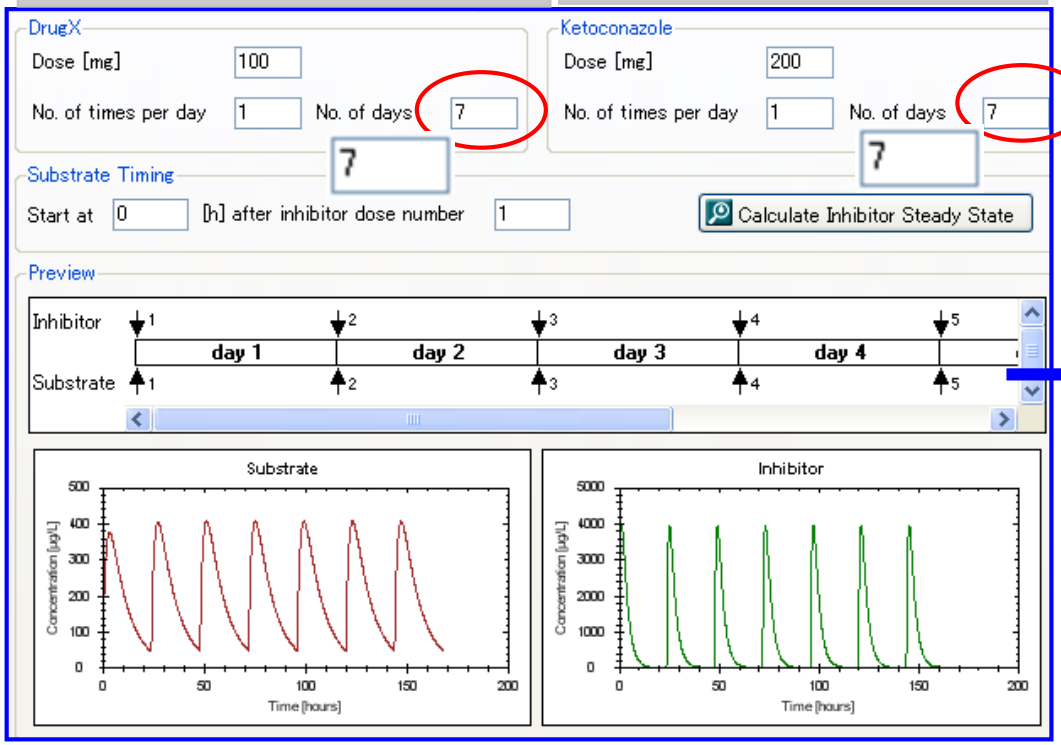
Repeated Dose Simulation (Competitive Inhibition Model)

Dosing Regimen

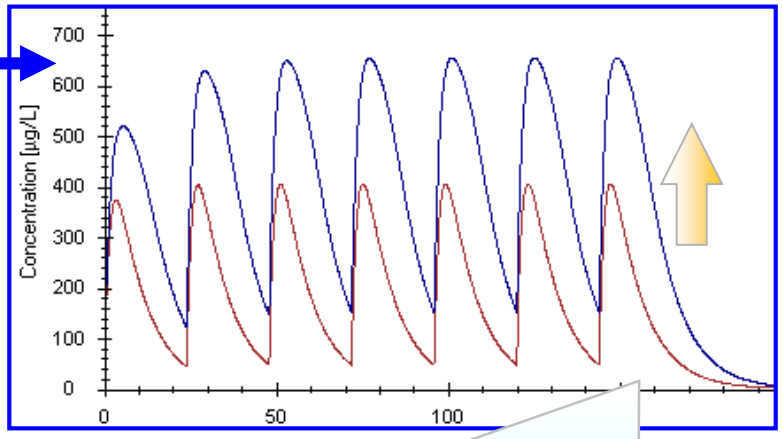
Substrate | **Inhibitor**



Results (*in vivo* Ki)

AUC ratio 1.9 → 2.1

Cmax ratio 1.4 → 1.6



Higher risk of DDI compared to single dose

2-2 Demonstration 2 (MBI)

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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 30μg/L)

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

(3) Coadministration with Metoprolol (2D6 substrate)

2-2 Demonstration 2 (MBI)

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Parameters used in simulation

(1) Calculated parameters

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

(2) *in vitro* data

fraction of 2D6 metabolism	$fm_{,2D6}$ = 0.86
apparent inhibition constant	Ki,app = 118.07 μg/L
max. inactivation rate constant	Kinact = 10.2 (h^{-1})

(3) Metoprolol dosing regimen

Twice a day (1 week) Dose = 60mg

2-2 Demonstration 2 (MBI)

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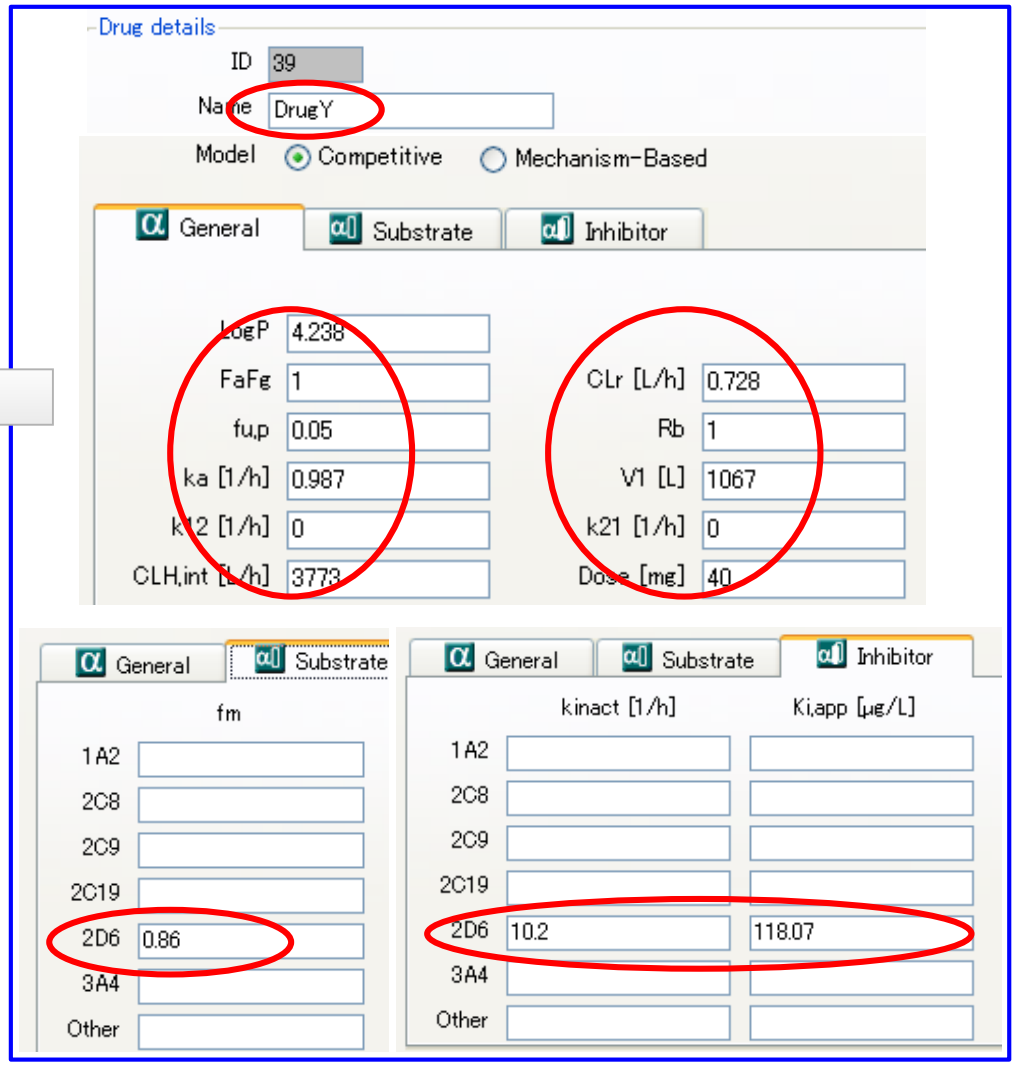
Parameter registration

DrugY parameters to be registered in DDI Simulator

PK parameters
in vivo Ki

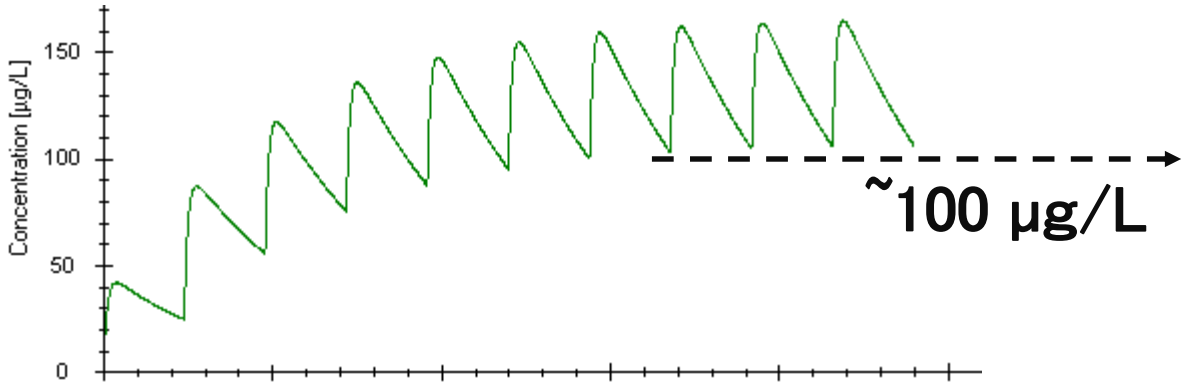


2-2 Demonstration 2 (MBI)

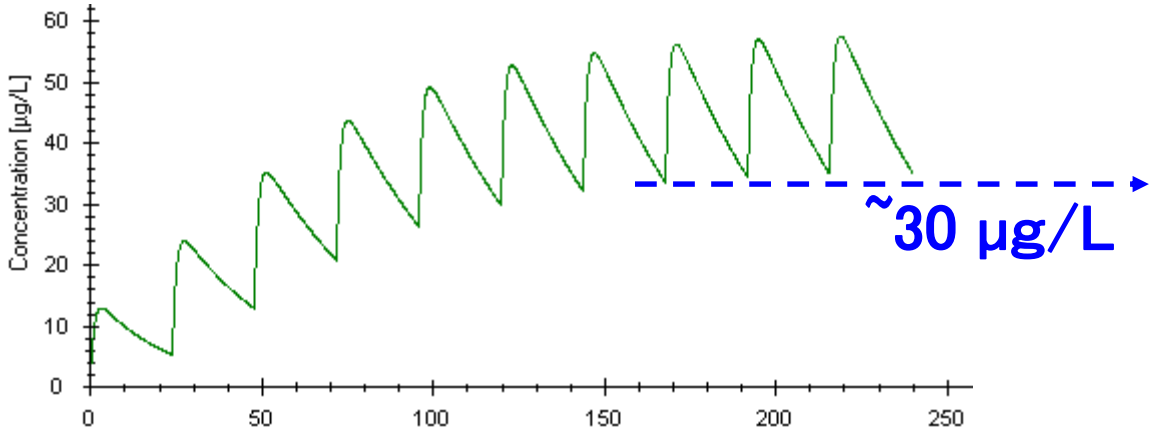
Optimized dosing regimen

Investigation of correct oral dose for DrugY in order to reach its effective blood concentration = 30μg/L

100mg/day
repeated
for 10 days →



40mg /day
repeated
for 10 days →



2-2 Demonstration 2 (MBI)

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Steady-state Calculations

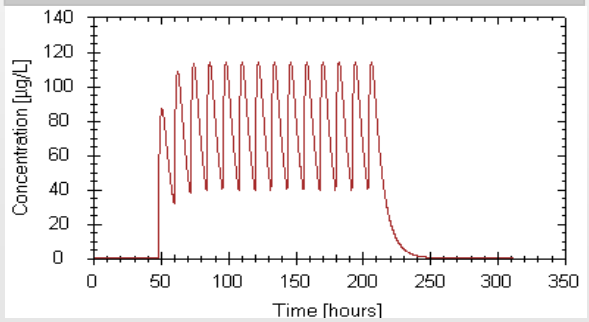
Metoprolol
Dose [mg] 60
No. of times per day 2 No. of days 7

DrugY
Dose [mg] 40
No. of times per day 1 No. of days 13

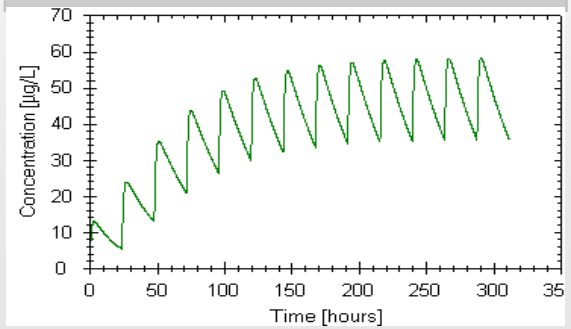
Substrate Timing
Start at 0 [h] after inhibitor dose number 3

Calculate Inhibitor Steady State

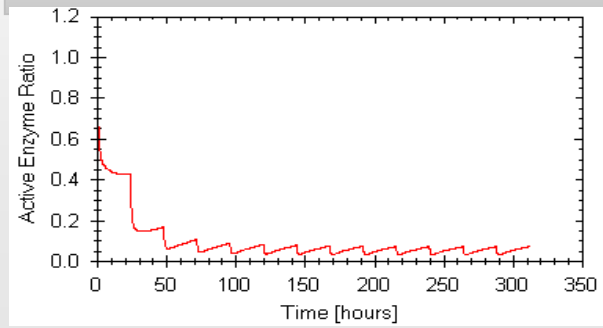
Metoprolol (Substrate)



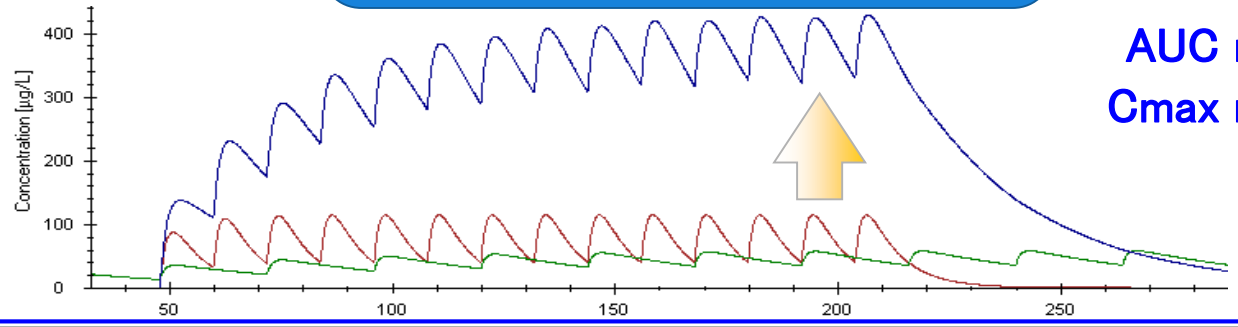
DrugY (Inhibitor)



Ratio of Active Enzymes(REact)



Predicted Results



AUC ratio 4.8
Cmax ratio 3.8

3. Future Plans

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DDI Simulator Future Enhancements

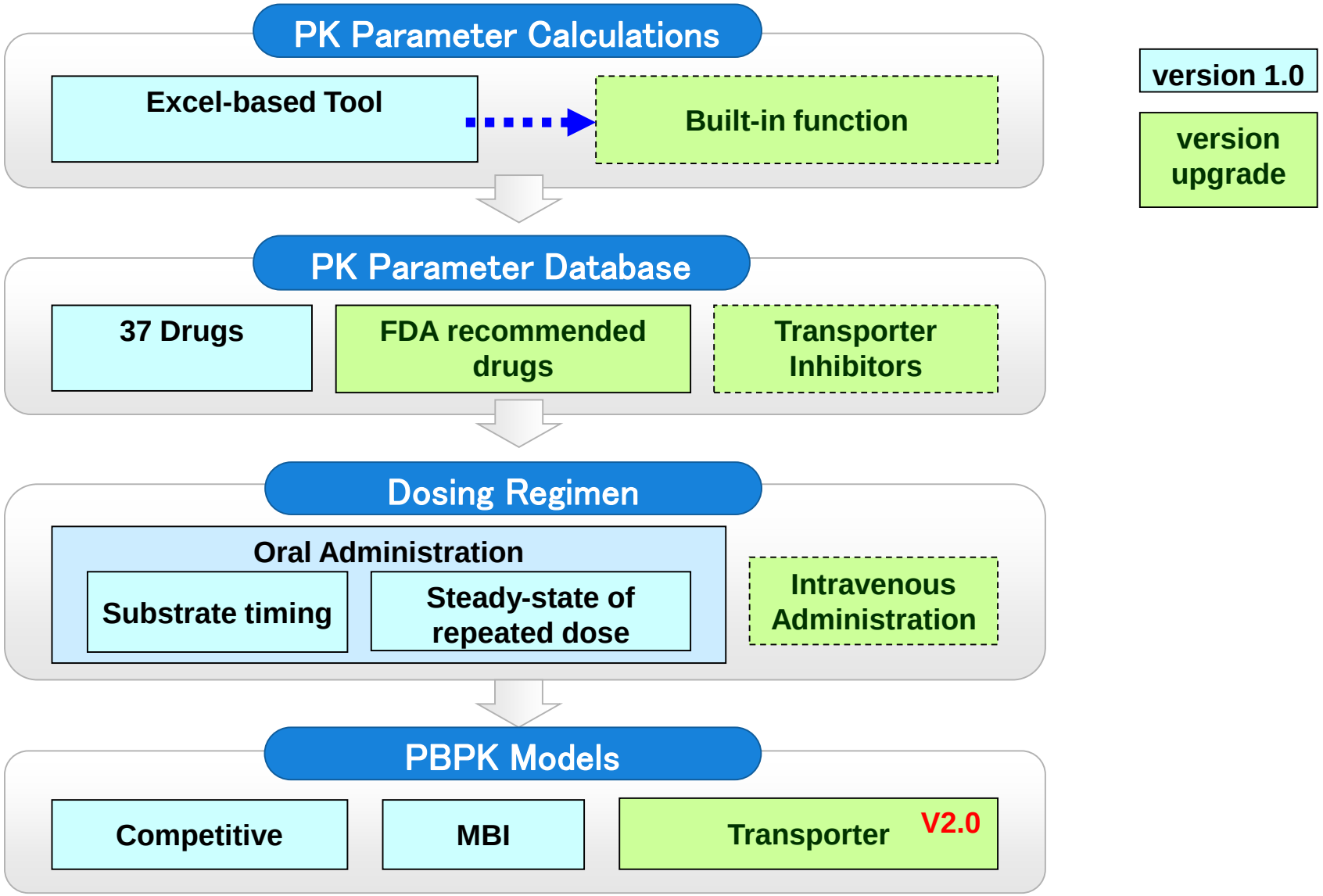
(1) Transporter model

(2) Data on FDA recommended drugs

(3) PK Parameter calculations

(4) Intravenous dosing simulations

3. Future Plans



3. Future Plans (New Drug Data)

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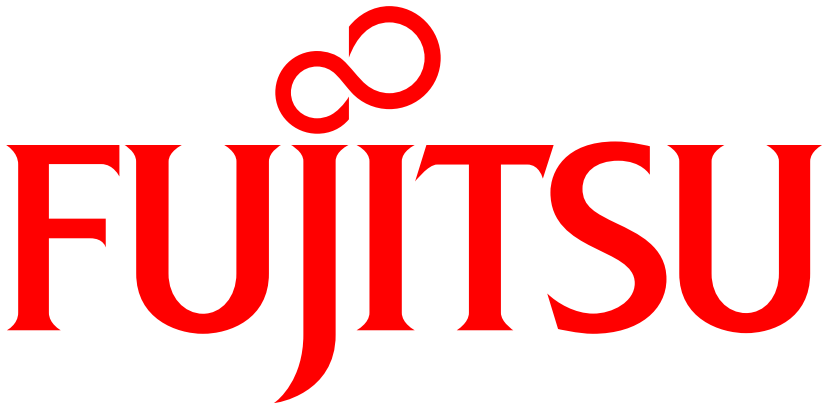
List of FDA recommended drugs for study of interactions

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



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