DDI Simulator(TM) V2.1

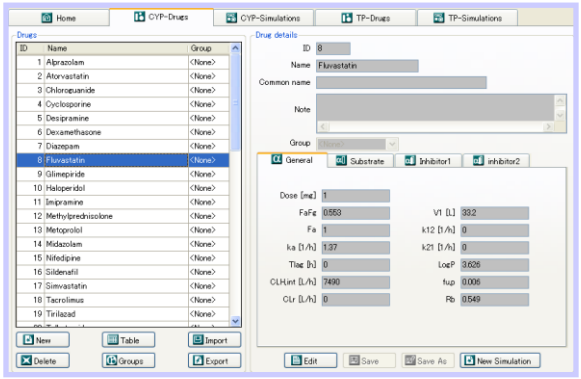
FUJITSU

DDI Simulator quantitatively predicts the extent of drug-drug interactions arising from co-administration of drugs, an important study in drug development, through time course simulation of the concentrations of each drug in the body using physiologically-based pharmacokinetic (PBPK) mathematical models.

DDI Simulator was developed based on the results of the Human Animal Bridging (HAB) Research Organization's Project in Japan. Development of new additional features, such as the database of drugs (containing in vivo Ki values), is currently under the supervision of Dr. Kazuya Maeda from the Graduate School of Pharmaceutical Sciences, University of Tokyo.

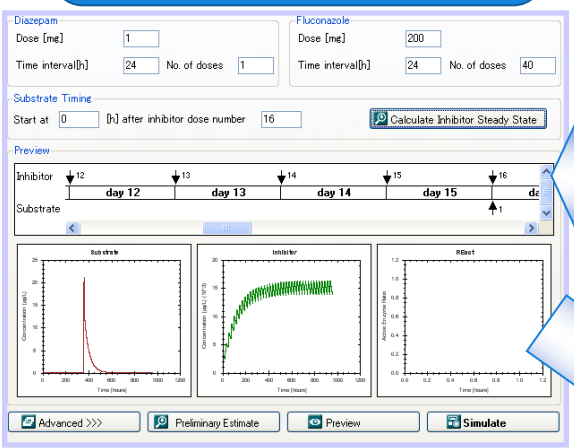
Simulation Flow

Add/Edit Drug PK data

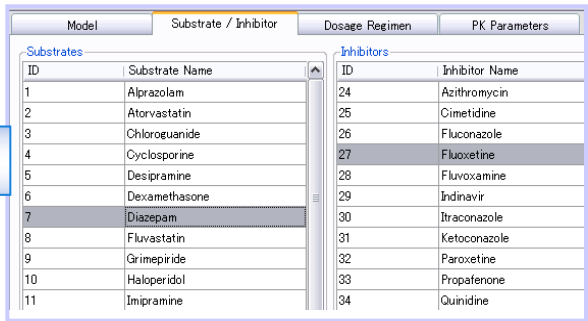


Choose a Simulation Model

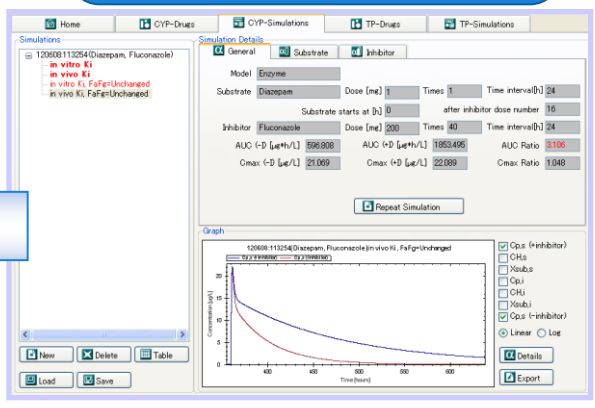
Set Dosing Regimen



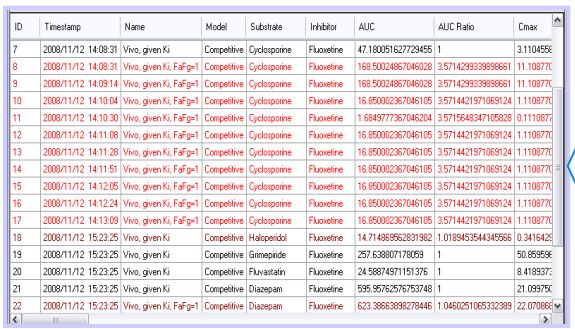
Select Substrate/Inhibitor



Run Simulations



Confirm Simulation Results

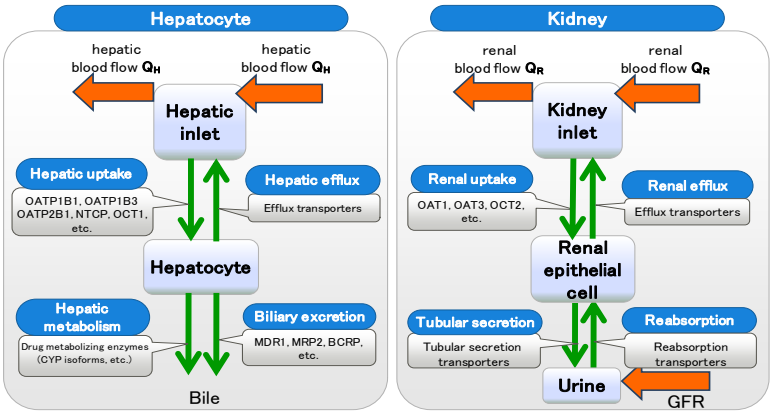


1. Enzyme(Competitive + MBI) and Transporter Inhibition models

Prediction of drug-drug interaction due to both enzyme inhibition and transporter inhibition is possible.

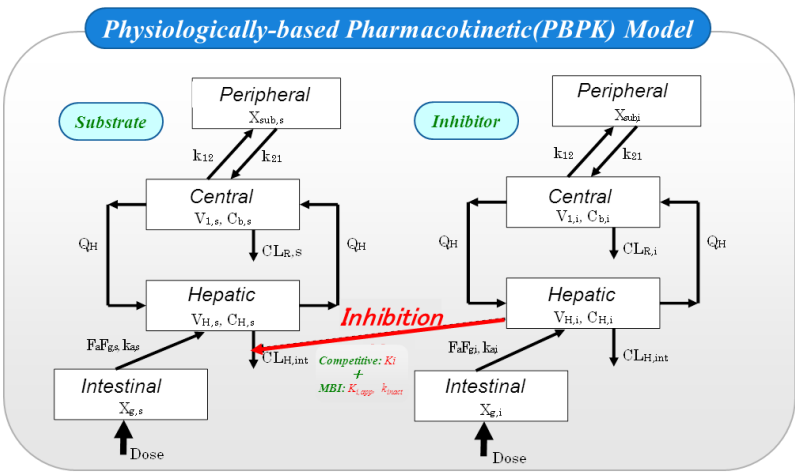
The ***enzyme inhibition*** model allows users to simulate simultaneous competitive and mechanism-based inhibitions that actually occur in clinical studies by integrating the two inhibition models into one.

The ***transporter inhibition*** model allows users to simulate simultaneous inhibitions of the metabolizing enzymes (competitive) and the uptake and/or efflux transporters in both the kidney and the liver.



2. Physiologically-based Pharmacokinetic Model

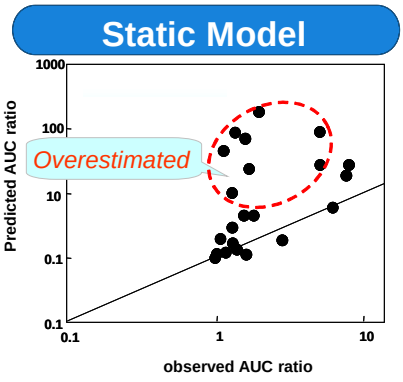
DDI Simulator uses PBPK models to simulate DDIs due to metabolizing enzyme and transporter inhibitions. The following shows the PBPK model used for the enzyme inhibition model (combined Competitive and MBI).

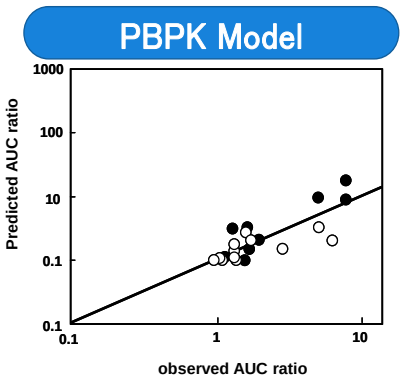


Advantages of using DDI Simulator

- ☑ **More accurate predictions than static models**
- ☑ **Allows prediction using in-house compound as inhibitor or substrate**
- ☑ **Evaluate risk based on AUC ratio, Cmax ratio or changes in elimination half-life**

As opposed to simple approximation by “1+[I]/Ki” where the concentration is constant, DDI Simulator uses PBPK model to simulate more accurate time-dependent concentrations. The comparison graphs below show several drugs give better agreement with experimentally observed results using the PBPK model.

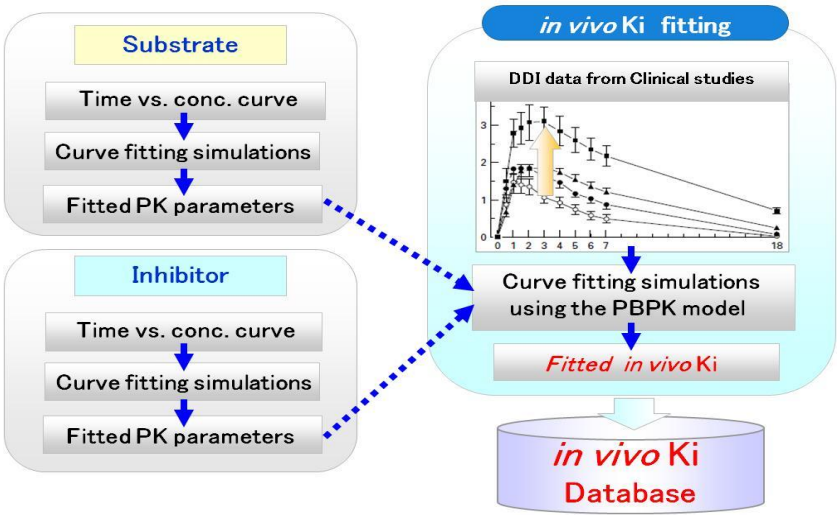




1. Kato M et al., Pharm Res. 25(8):1891−1901(2008)

3. Drugs Database (includes drugs in the FDA 2012 revised draft guidance)

The database contains a total of 77 drugs (Substrate 47 drugs and Inhibitor 30 drugs) which includes FDA-recommended[*5] substrates and inhibitors for study in all major CYP isoforms (1A2, 2C8, 2C9, 2C19, 2D6, 3A4) making it possible for users to readily simulate DDI with their own compounds. The registered inhibitors contain human *in vivo* Ki values obtained by parameter optimization using actual data from DDI clinical studies. For in-house drugs in pre-clinical phase where *in vivo* Ki is unknown, accurate prediction of *in vivo* Ki from *in vitro* Ki is possible based on a formula using only the octanol-water partition coefficient (logP) .

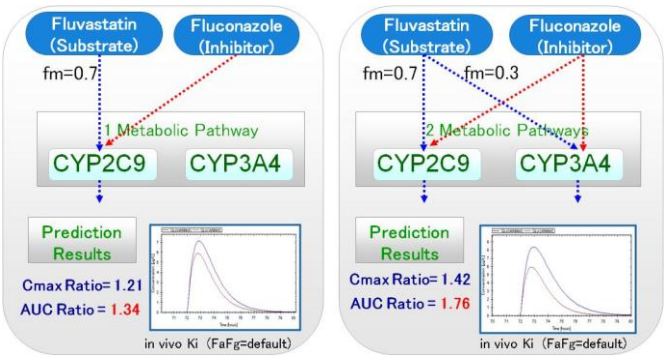


4. Inhibition of Multiple CYP Isoforms

Accurate prediction of DDI is possible for drugs metabolized by several CYP isoforms. By simply assigning each CYP's contribution to the total metabolism of the substrate, the effect of simultaneous inhibition of multiple CYP isoforms can be studied.

Clinically observed AUC Ratio = 1.84

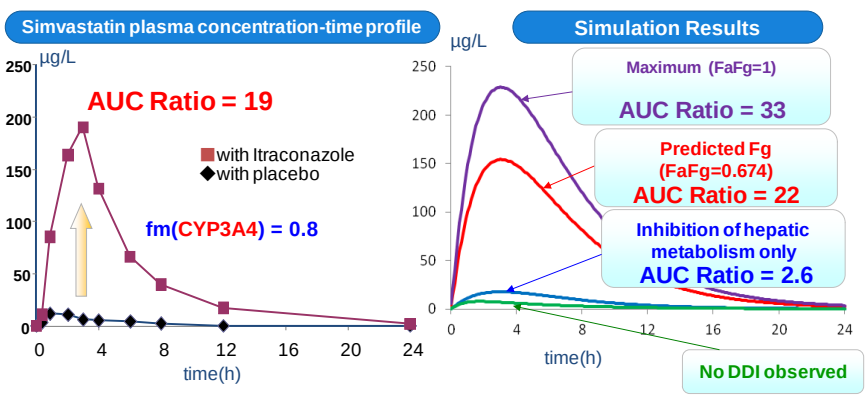
2.Kantola T et al., Eur J ClinPharmacol. 56(3):225-9(2000)



5. Inhibition of Intestinal Metabolism

Drug metabolizing enzymes like CYP3A4 exists not only in the liver but also in the small intestines. Inhibition may occur in both places that would affect the risk level of DDI.

Accurate prediction of the increase in FaFg (when intestinal metabolism is inhibited) reduces overestimated predictions of DDI as compared to setting the FaFg to a maximum value (FaFg=1).



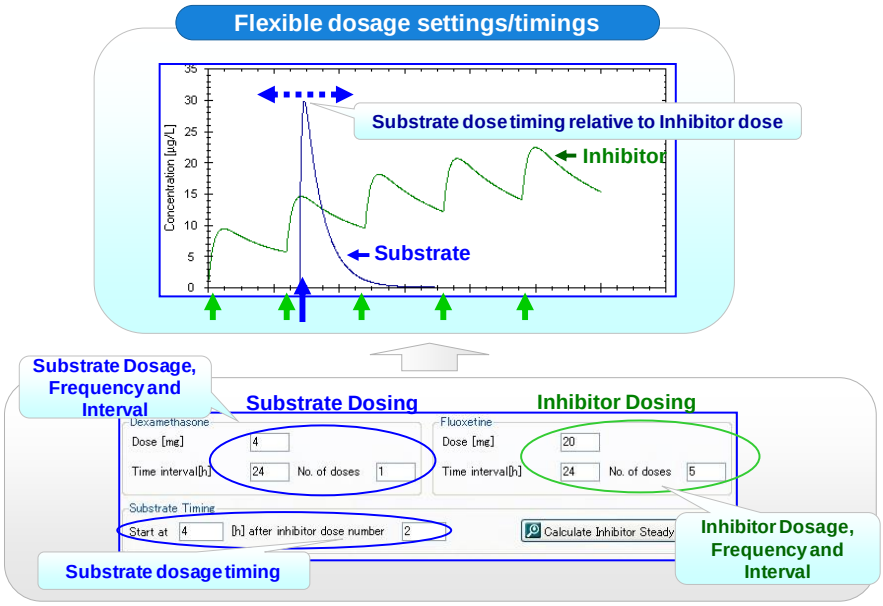
3.Neuvonen PJ et al., Clin Pharmacol Ther. 63(3):332-41(1998)

6. Optimization of Dosing Regimen to Minimize Risk

Flexible settings allow the user to study the best dosing regimen for both the substrate and the inhibitor in order to minimize the risk of DDI. Also, simulation of the maximum risk when administering repeated doses of the inhibitor is automatically done by calculating the right substrate dose timing at the steady-state.

[Dosing Regimen Settings]

- Dose
- Time interval
- No. of doses
- Substrate dose timing



System Requirements

OS	: Windows® XP, Windows Vista®,Windows® 7, Windows® 8
CPU	: 1.0GHz or higher（2.0GHz or higher recommended）
Memory	: 1.0GB or higher（2.0GB or higher recommended）
Hard disk space	: 1.0GB or higher

References

1.Kato M, Shitara Y, Sato H, Yoshisue K, Hirano M, Ikeda T, Sugiyama Y.
The quantitative prediction of CYP-mediated drug interaction by physiologically based pharmacokinetic modeling.
Pharm Res. 2008 Aug;25(8):1891-901.

2.Kantola T et al., Effect of fluconazole on plasma fluvastatin and pravastatin concentrations.
Eur J ClinPharmacol. 56(3):225-9(2000)

3.Neuvonen PJ et al., Simvastatin but not pravastatin is very susceptible to interaction with the CYP3A4 inhibitor itraconazole.
Clin Pharmacol Ther. 63(3):332-41(1998)

4. Enzyme- and Transporter-Based Drug-Drug Interactions Progress and Future Challenges Springer
Chapter 12 Extrapolation of In Vitro Metabolic and P-Glycoprotein-mediated Transport Data to In Vivo by Modeling and Simulations AAPS Press. 2010:299-307,311-315.

5. FDA Guidance for Industry, Drug Interaction Studies ― Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (Draft Guidance, February 2012)

Developed by

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