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Admetry® User Manual

Pharmacokinetic and Drug Metabolism Data Analysis for Everyone

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Admetry® User Manual

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Admetry® is a user friendly software for pharmacokinetic/toxicokinetic and drug metabolism data analysis. It is ideal for those who are new to pharmacokinetics and drug metabolism but also DMPK experts who prefer to perform PK calculations and drug metabolism analysis in an intuitive interface.

PK/TK Analysis	Calculates standard PK parameters (C_{max}, AUC, half-life,…) and compares user drug candidate against 500 marketed drugs in humans.	**Drug-Drug Interaction**	Quickly references FDA preferred and accepted substrates, inhibitors, and inducers of CYP450 isoforms with chemical structures provided.
Metabolite ID	Calculates potential metabolite ions resulting from phase I and phase II metabolic reactions for LC/MS analysis. Includes example reaction structures.	**In Vivo Clearance Prediction**	Projects in vivo hepatic clearance based on in vitro S9, microsome, and hepatocyte data.
Allometry	Projects and compares half-life, clearance, or volume of distribution values across multiple species.	**Drug Metabolite Scan**	Automatically identifies potential Phase I and Phase II metabolites. *Additional software license is required.*
Human Pharmacology Database	Queries a human pharmacokinetics database of 500 marketed drugs for half-life, volume of distribution, clearance, and chemical structures.	**IC50 Determination**	Calculates IC_{50} values and graphs inhibition data
Human Equivalent Dose	Calculates the human equivalent dose from any animal model based on body surface area and body weight.	**DDI Non-competitive/ Competitive**	Calculates drug-drug competitive and non-competitive interactions using 4 different models.

Getting Started 2

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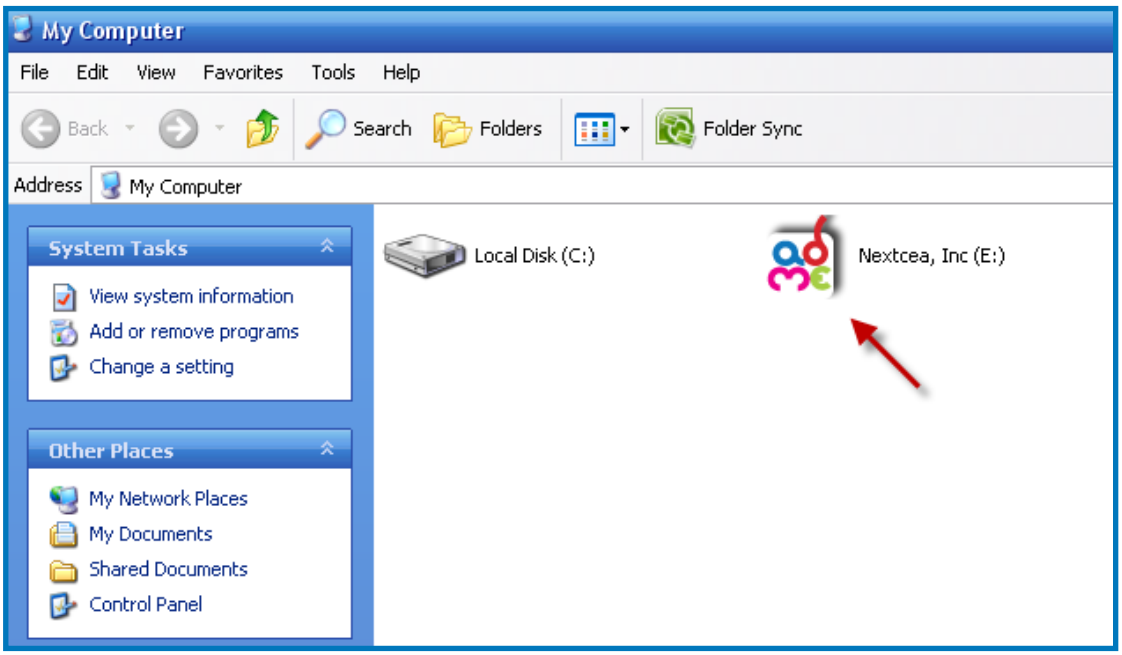
2.1 Installing Admetry®

Installing Admetry® is easy. Admetry® Setup Wizard will start automatically upon inserting CD.

If Setup Wizard does not start automatically:

- Insert Admetry® CD
- Open "My Computer"
- Double click Admetry® Setup icon



Getting Started 2

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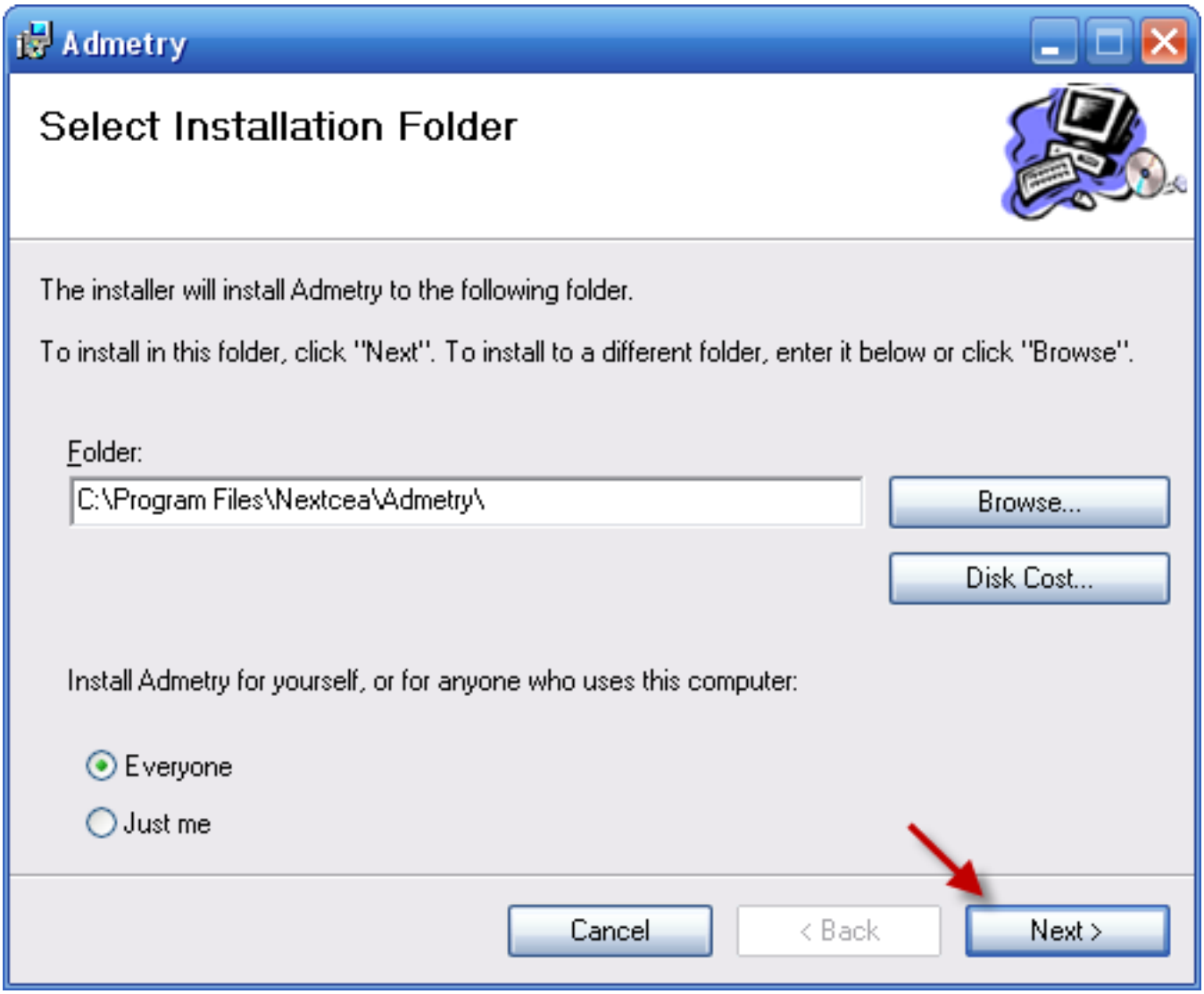
- Click "Next"

Getting Started 2

2.2 Select Installation Folder

- Specify the directory where Admetry® will be installed
- Choose “Everyone” or “Just me” installation options depending on who will be using Admetry®
- Click “Next”



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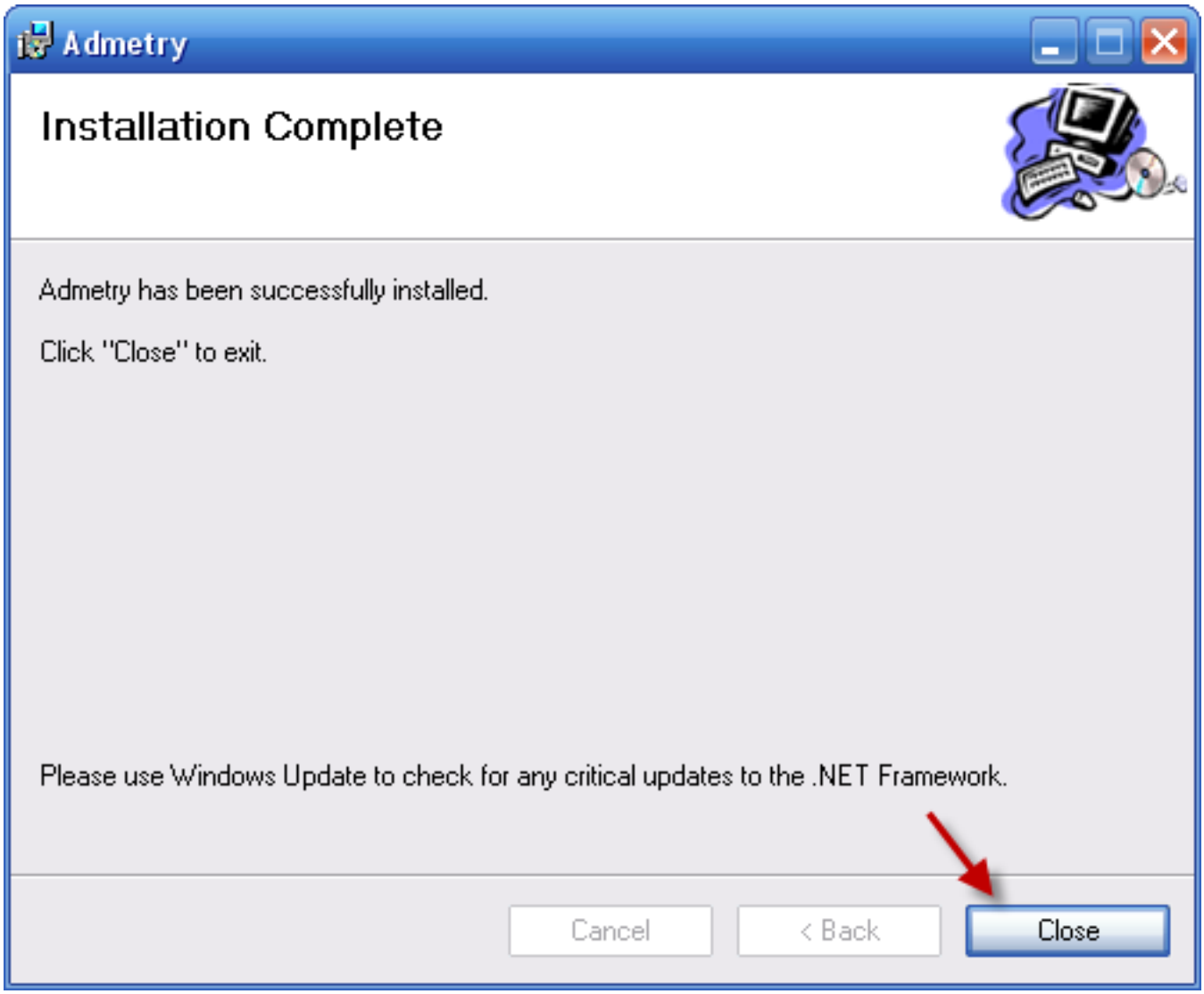
2.3 Completing Installation

- Admetry will install (please be patient as it normally takes a few minutes)

Note: Microsoft .NET Framework version 3.5 is required. If you do not have Microsoft .NET Framework 3.5, Admetry will install it to your computer automatically.

- Click "Close" to complete the installation



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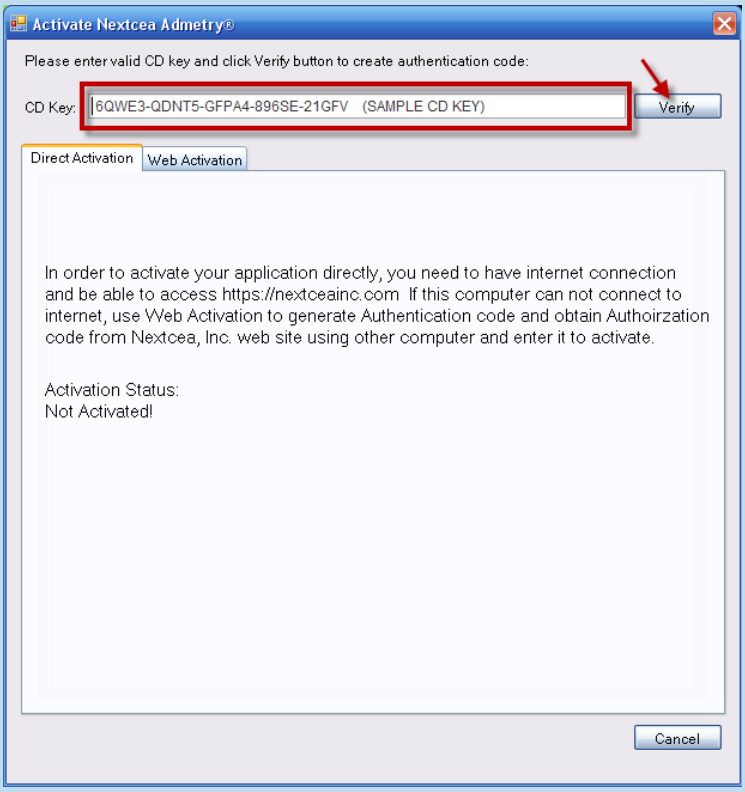
Activating Admetry®

When Admetry® first opens after installation you will be prompted to activate the software. You can activate Admetry® via **Direct Activation** or **Web Activation**.

After purchasing an Admetry® license, Nextcea will email you an activation CD key.

2.4 **Direct Activation** (for computers with internet connection)

- Type in CD Key obtained from Nextcea to activate Admetry®
- Click "Verify"



Please allow a few minutes to connect to Nextcea's server for activation.

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- If activation is successful, "Activation Status" will read "Activated"
- If activation is not successful, the CD key may already be registered.

Please note that each CD key is only allowed to be installed onto one computer per license.

Email Admetry@nextcea.com should you experience any problems during activation.

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2.5 Web Activation (for computers with limited internet access)

Web activation is intended for computers with internet activation problems due to firewall, limited internet access, or no internet access.

Note: This method requires a **flash drive** to transfer small files

1. Type or Paste in the CD Key found in the Admetry® activation email from Nextcea.

2. An **authentication code** will be generated in the text box.
Click "Copy Authentication Code" to copy the code to your clipboard.

3. Paste the **authentication code** into Notepad and save the file on a flash drive.

4. On a computer with internet access, log onto:
https://nextcea.com/web/PkTk/PublicContent/AuthorizeAdmetry.aspx

5. Copy and paste the authentication code into the textbox labeled "Please enter your authentication code". Click "Submit".

6. Copy the **Authorization Code** from the textbox below and paste it back into Notepad and save it on the flash drive. Return the flash drive to the original computer with Admetry® installed and paste the **Authorization Code** into the Authorization Code textbox.

7. Click "Activiate Admetry".

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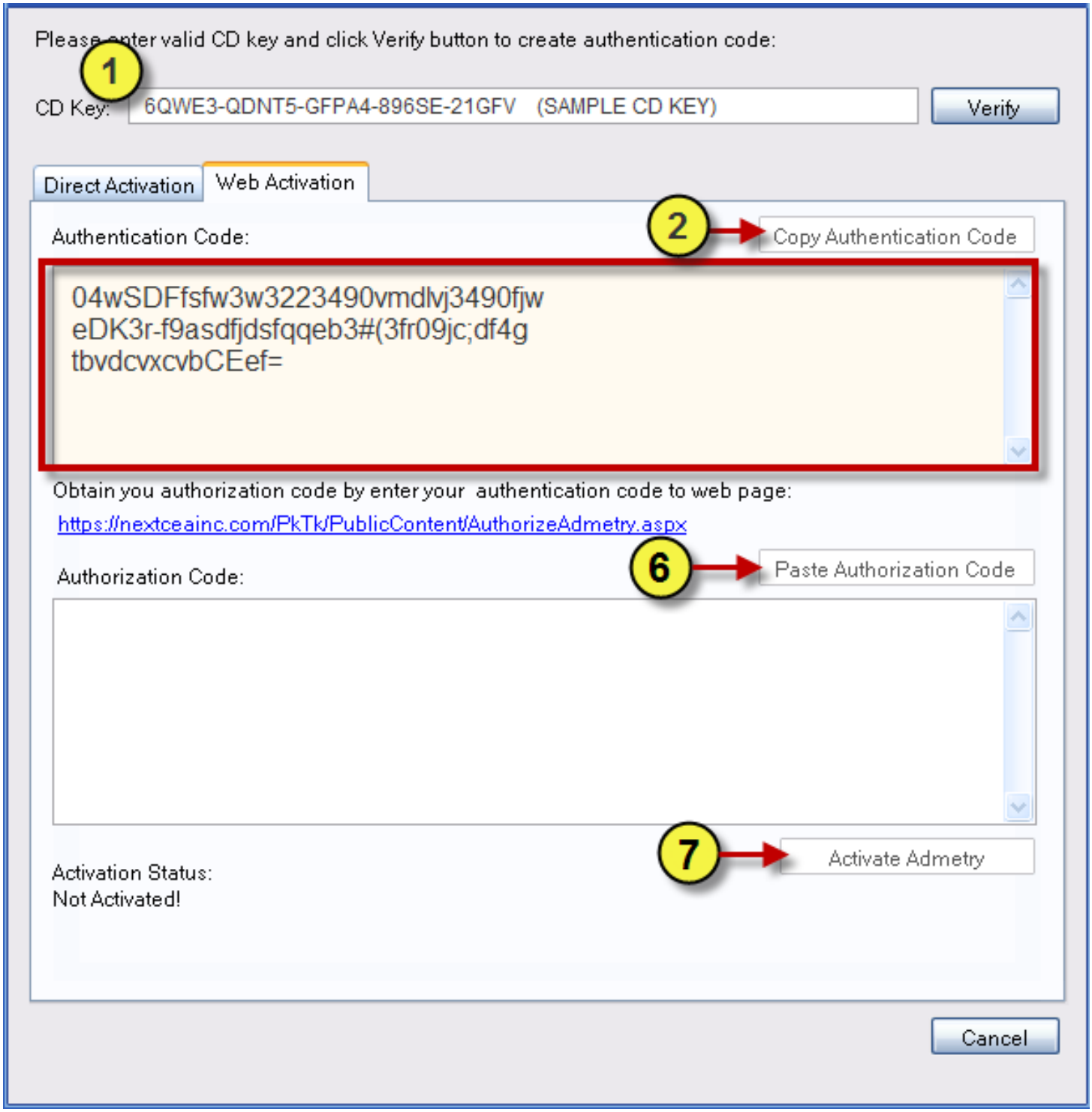

Admetry® should now be activated. If activation is not successful, the CD key may already be registered. Email Admetry@nextcea.com should you experience any problems during activation.

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(Step 5. Obtaining the **Authorization Code** through Nextcea's website)

If activation is successful, Activation Status will read "Activated"

If activation is not successful, the CD key may already be registered. Email Admetry@nextcea.com should you experience any problems during this step.

Pharmacokinetic and Toxicokinetic Analysis 3

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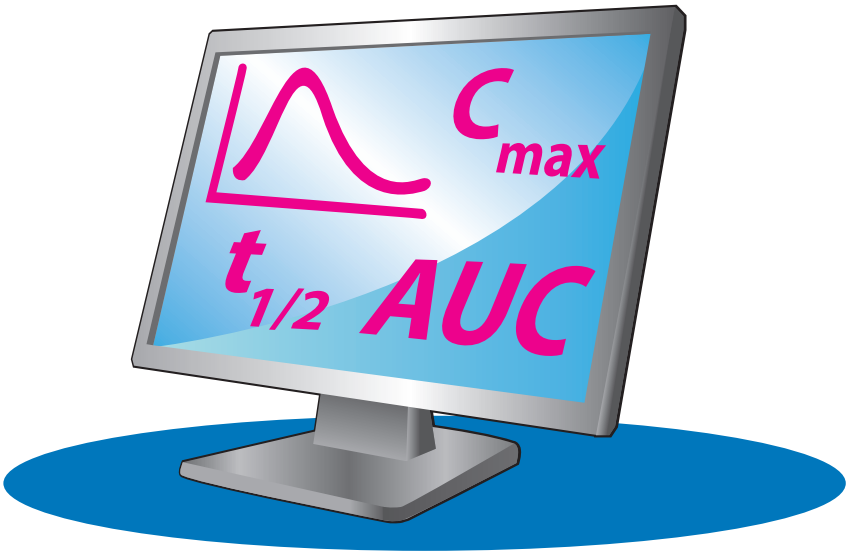
3.1 About PK/TK Analysis



PK/TK Analysis includes modules for single, repeat, and multiple-dose analysis and calculations are based on non-compartmental models. Intravenous (IV) or extra-vascular (ie. oral, subcutaneous, topical, inhalation, rectal or percutaneous) dose analysis are available. Concentration-time data can be entered manually or imported from Excel using the data paste function. The results are presented graphically and in list form.

3.2 Enter dosing regimen

- Enter Study Protocol/Title (optional)
- Select animal species and gender (optional)

Note: If animal species **is not** selected, the resulting PK parameters will be displayed in "per kg" units. If animal species **is** selected, the resulting PK parameters will include "per m^2" in addition to "per kg".

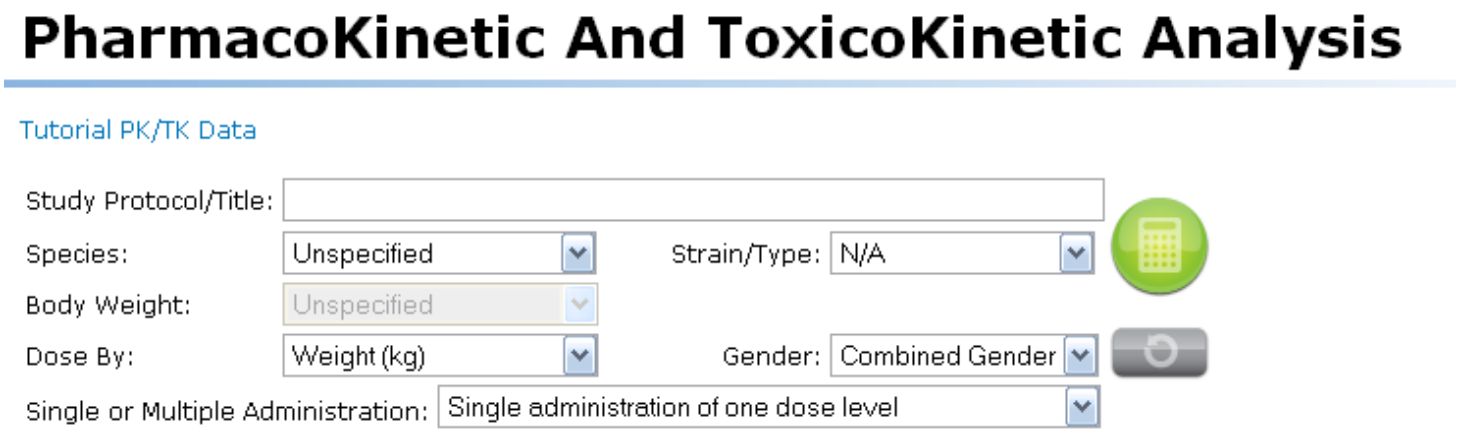
Units *without* species selected

V_z	52.8	mL/kg
V_{ss}	36.6	mL/kg
CL	5.91	mL/hour/kg

Units *with* species selected

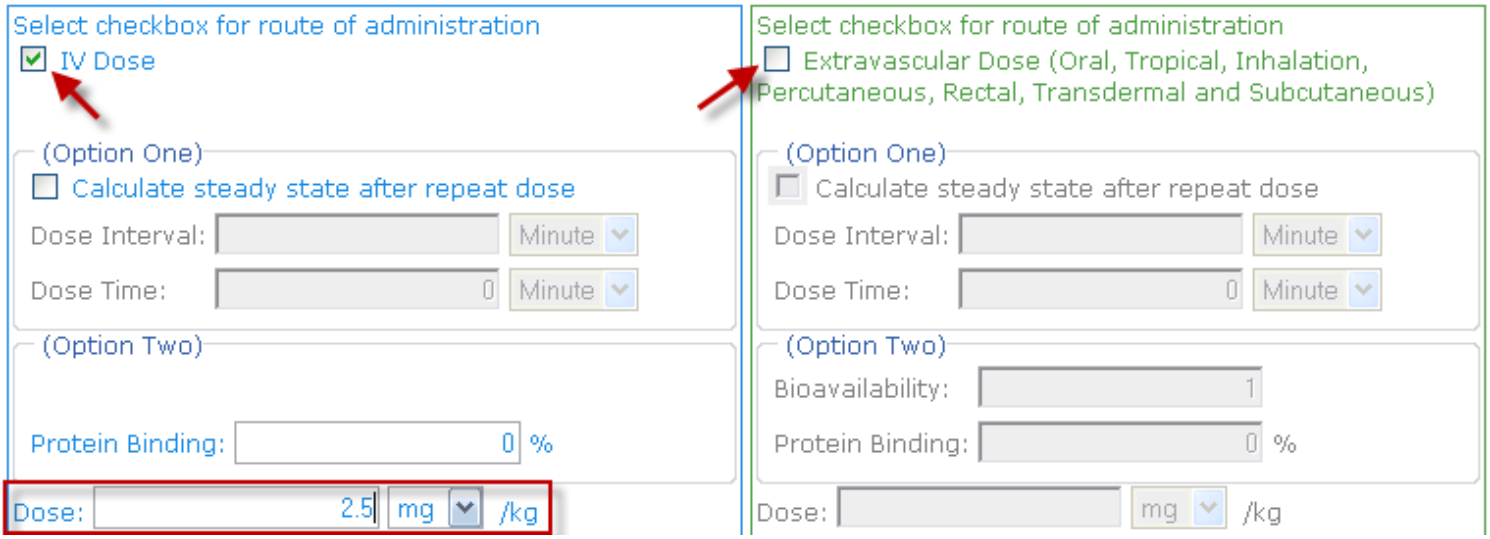
V_z	52.8	mL/kg
	158	mL/m^2
V_{ss}	36.6	mL/kg
	110	mL/m^2
CL	5.91	mL/hour/kg
	17.7	mL/hour/m^2

- Select standard body weight or enter a specified body weight (optional)
- Select single, repeat, or multiple-dose regimen
- Select dose by weight or surface area



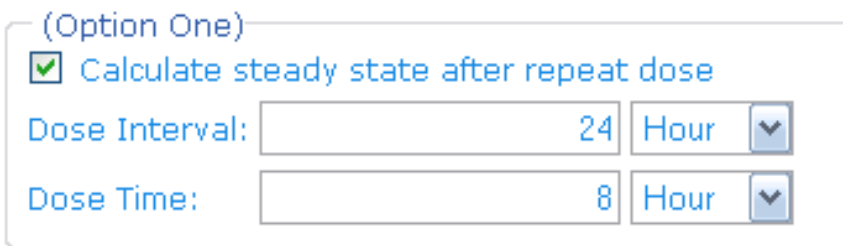
3.3 Enter route of administration and dosing level

- Select IV and/or Extravascular Dose checkbox for route of administration
- Specify the dose level



3.4 Calculate steady state (optional)

- Select checkbox for steady state calculation after repeat dose
- Enter dose interval and time

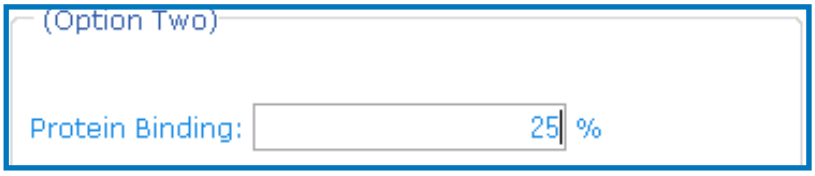


3.5 Protein binding (optional)

Inputting protein binding data from dialysis studies is strongly recommended to accurately determine in vivo and in vitro PK parameters. If protein binding data is not included, Admetry® defaults protein binding as 0%.

When preparing samples for PK analysis the drug extraction procedure artificially dissociates the drug from plasma/serum proteins (ie. protein binding = 0%) by organic solvents (acetonitrile, methanol).

- Specify protein binding (%)



3.6 Bioavailability (optional)

Inputting bioavailability data is also strongly recommended to accurately determine in vivo and in vitro PK parameters. If bioavailability data is not included, Admetry® defaults bioavailability as 100%.

- Specify bioavailability if known (oral administration only)
- Determine bioavailability by following the steps in Section 3.14

3.7 Bio-analytical data requirements

The bio-analytical data requirements for single, repeat and multiple/repeat-dose analysis are listed below.

- Single administration of one dose level (Time, Concentration)
- Single-dose with one different levels (Dose Level, Time, Concentration)
- Multiple/Repeat-dose with different dose levels (Dose Level, Schedule, Time, Concentration)

Admetry® recognizes the term "BLQ" as a concentration below the limit of quantitation. It does not convert "BLQ" concentration entries to zero. Instead, Admetry® excludes data points with "BLQ" concentrations in all PK/TK parameter calculations.

When inputting bio-analytical data for single oral dose, the first data point should be time= 0, concentration= 0.

3.8 Enter bio-analytical data

Bio-analytical data may be entered for single or multiple patients/animals. Enter data for multiple animals sequentially. As an example, enter all concentration-time data for patient one followed by all concentration-time data for animals two and three. Concentration entries of matching time points are averaged prior to PK/TK analysis.

- Enter bio-analytical data manually or with the Paste Bio-analytical Data function

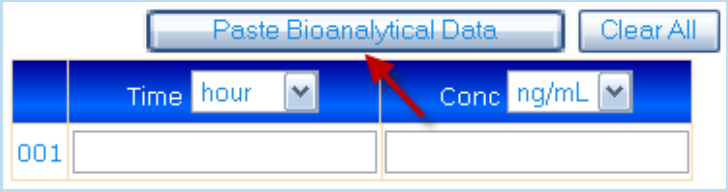
Pharmacokinetic and Toxicokinetic Analysis 3 Nextcea

How to input bio-analytical data from Excel:

- Copy data from Excel spreadsheet

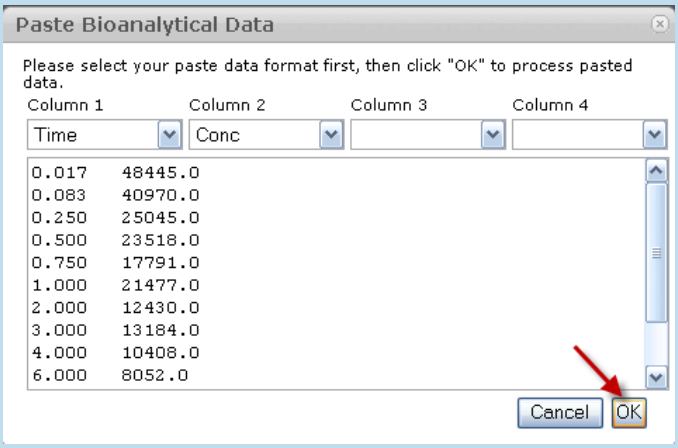
	A	B	C	D
1	Single Administration of One Dose Level			
2				
3	IV			
4	Dose	1	mg/kg	
5				
6	Time (hr)	Conc (ng/mL)		
7				
8	0.017	48445.0		
9	0.083	40970.0		
10	0.250	25045.0		
11	0.500	23518.0		
12	0.750	17791.0		
13	1.000	21477.0		
14	2.000	12430.0		
15	3.000	13184.0		
16	4.000	10408.0		
17	6.000	8052.0		
18	24.000	321.0		
19	48.000	233.0		
20				
21				

- In Admetry® window click "Paste Bioanalytical Data"



- Identify the columns and click "OK"

(Note: As a default, Column 1 is set to "Time" and Column 2 is set to "Conc")



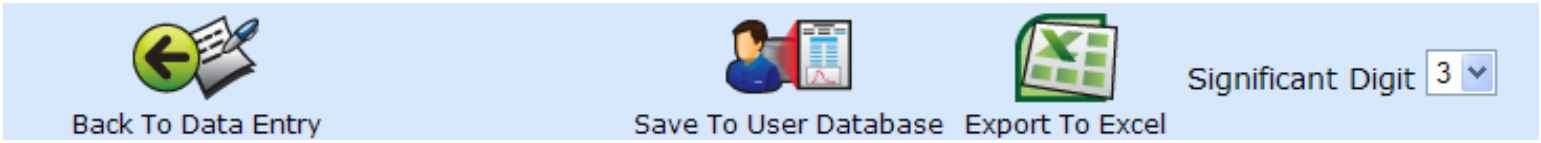
3.9 Submit analysis

- Click  to perform PK/TK analysis
- View results

To reset ALL data input, click 

3.10 Editing data after viewing results

- Click "Back To Data Entry" in the PK/TK Analyzer results page to return to data entry
- Click "Save To User Database" and enter in a brief description of the results
- Click "Export To Excel" to save data in Microsoft Excel format



3.11 PK/TK Parameter Tables and Graphics

PK/TK parameters are viewed in downloadable tables and graphics. Users can select the number of significant digits to report.

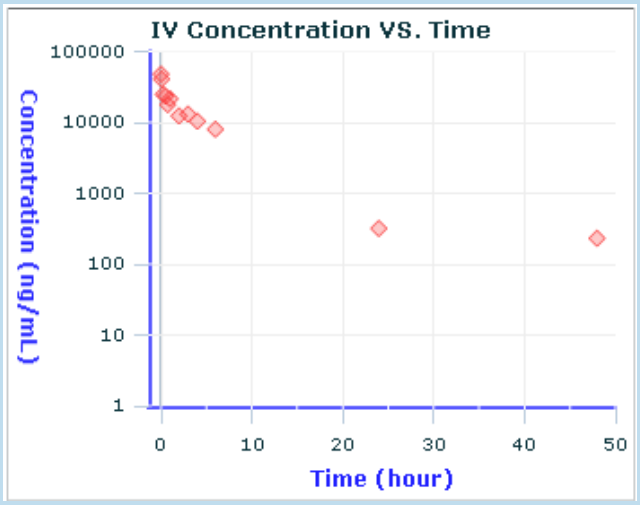
3.12 Single-dose results

PK/TK Parameters

IV Dose Parameters

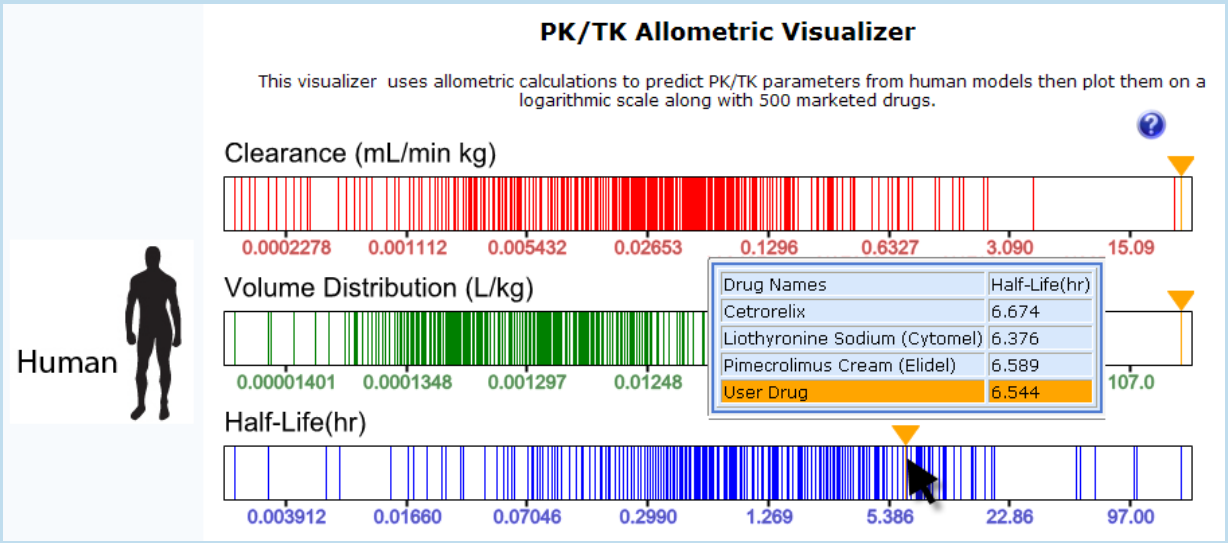
Parameter Name	Value	Unit
Dose Level	5.00	mg/kg
Protein Binding	0.00%	
C_0	5.06e+4	ng/mL
C_{max}	4.84e+4	ng/mL
t_{max}	0.0170	hour
$t_{1/2}$(Terminal Phase)	6.54	hour
$t_{1/2}$(Distribution Phase)	0.273	hour
$AUC_{(0-t)}$	1.67e+5	hour*ng/mL
AUC_{∞}	1.70e+5	hour*ng/mL
$AUMC_{(0-t)}$	9.27e+5	hour*hour*ng/mL
$AUMC_{\infty}$	1.05e+6	hour*hour*ng/mL
MRT	6.21	hour
V_z	278	mL/kg
	835	mL/m^2
V_{ss}	183	mL/kg
	549	mL/m^2
CL	29.5	mL/hour/kg
	88.4	$mL/hour/m^2$
C_{max}/Dose	9.69e+3	(ng/mL)/(mg/kg)
	2.91e+4	$(ng/mL)/(mg/m^2)$

Drug concentration vs. time graph



PK/TK Allometric Visualizer

The calculated PK values from all different animal species are allometrically converted to human PK values and then compared against 500 marketed drugs in the human clinical PK database.



Volume of Distribution & Clearance Meter

Displays 3 levels (low, medium, high) of each species. Volume of distribution meter is determined by intracellular + extracellular fluid (total body fluid) in individual animal species. Clearance meter is determined by the total blood flow of liver and kidneys in individual animal species.

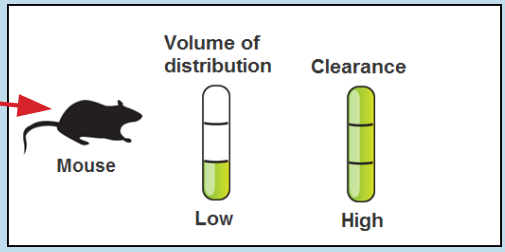
Volume of Distribution

Low = <30% total body fluid
Medium = >30% and <70% of total body fluid
High = >70% of total body fluid

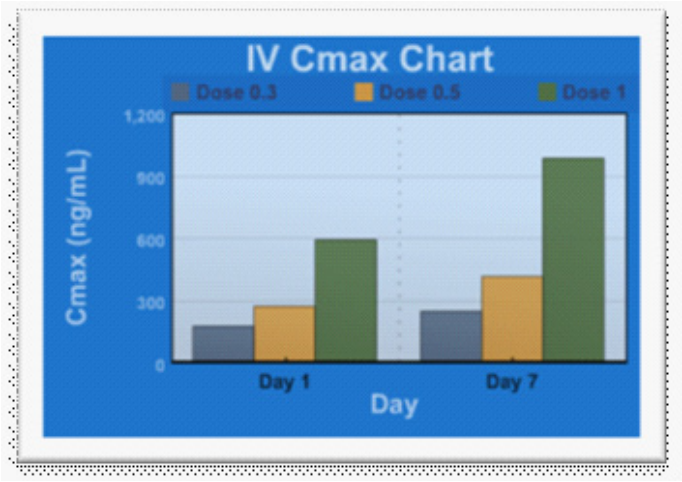
Clearance (Hepatic + Renal)

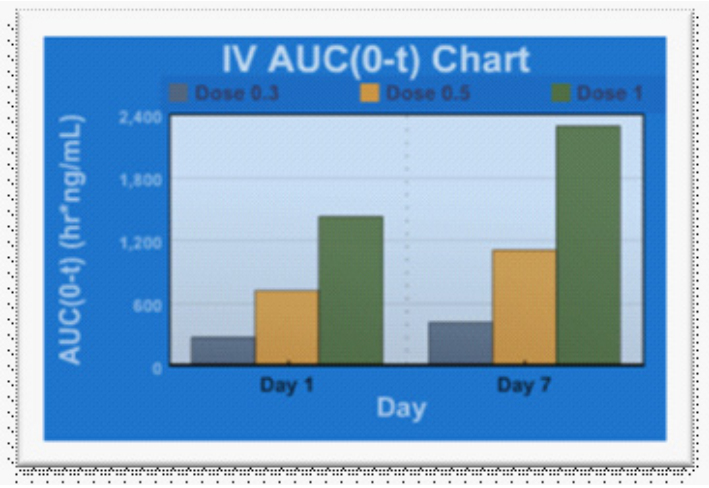
Low = <30% total blood flow
Medium = >30% and <70% of total blood flow
High = >70% of total blood flow

An animal icon will be displayed when an animal species is selected during data entry.



3.13 Multiple/Repeat-dose results





3.14 Determining Bioavailability

- Select checkboxes for both IV and extravascular routes of administration (ie. oral, topical, subcutaneous etc...)
- Enter IV and extravascular routes dose levels and bio-analytical data into Admetry®

- Click calculate button 
- Bioavailability is reported in the PK/TK parameters table

PharmacoKinetic / ToxicoKinetic Parameters

IV Dose Parameters

Parameter Name	Value	Unit
Dose Level	1.00	mg/kg
Protein Binding	0.00%	
C_0	0.00	ng/mL
C_{max}	4.84e+4	ng/mL
t_{max}	0.0170	hour

Oral Dose Parameters

Parameter Name	Value	Unit
Dose Level	5.00	mg/kg
Protein Binding	0.00%	
Bioavailability (F)	1.65%	
C_0	0.00	ng/mL
C_{max}	902	ng/mL
t_{max}	4.00	hour

Clinical Pharmacological Database 4

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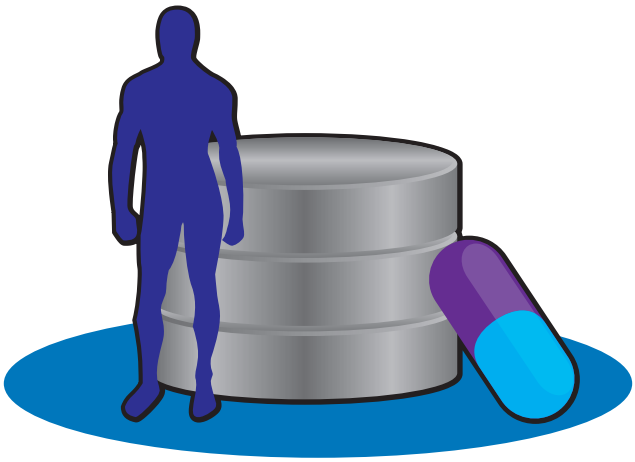
4.1 About Clinical Pharmacological Database



The clinical pharmacological database contains 500 marketed drug compounds in humans. Users can instantly find valuable human PK parameters based on a variety of search options. By pointing to a drug, the structure, chemical formula, therapeutic class, human PK (ie. bioavailability, clearance,...) will be displayed.

Clinical Pharmacology Database

Half Life (hr): 1 to 2 Search

Volume of Distribution (L/kg): 1 to 2

Clearance (mL/min*kg): to

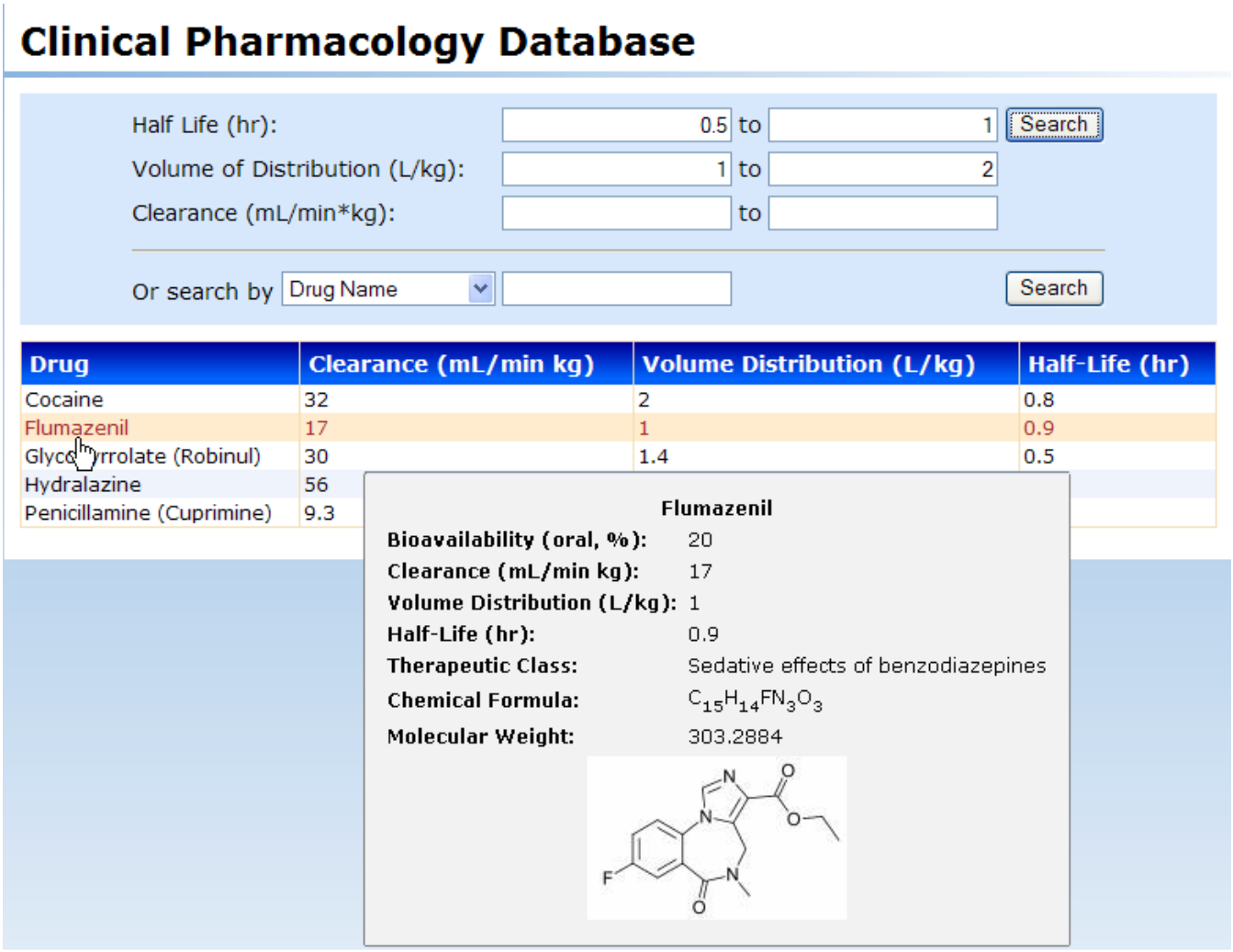
Or search by Drug Name Search

Drug	Clearance (mL/min kg)	Volume Distribution (L/kg)	Half-Life (hr)
Benzocaine	21.2	1.04	1.75
Cefotaxime (Claforan)	7.5	1.2	1.2
Cimetidine (Tagamet)	8.3	1	2
Cromolyn (Opticrom)	15.6	1.8	1.3
Didanosine (Videx)	16	1	1.4

Clinical Pharmacological Database 4

4.2 Using Clinical Pharmacological Database

- Input a range of search values for either Half Life, Volume of Distribution, and/or Clearance
- Type in drug name (optional)
- Click "Search"
- Scroll over compounds to view the PK parameters and drug information



Human Equivalent Dose Calculation 5

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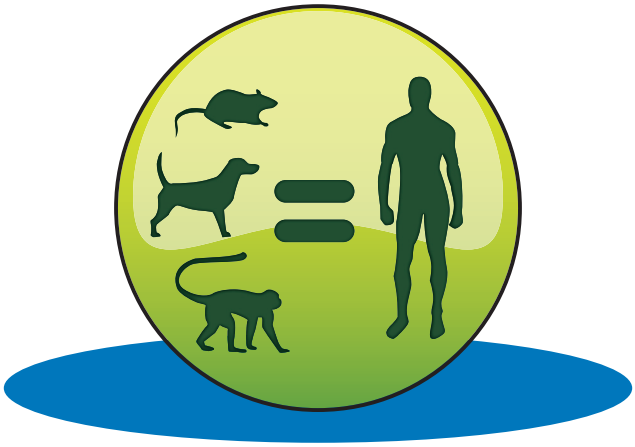
5.1 About Human Equivalent Dose Calculation

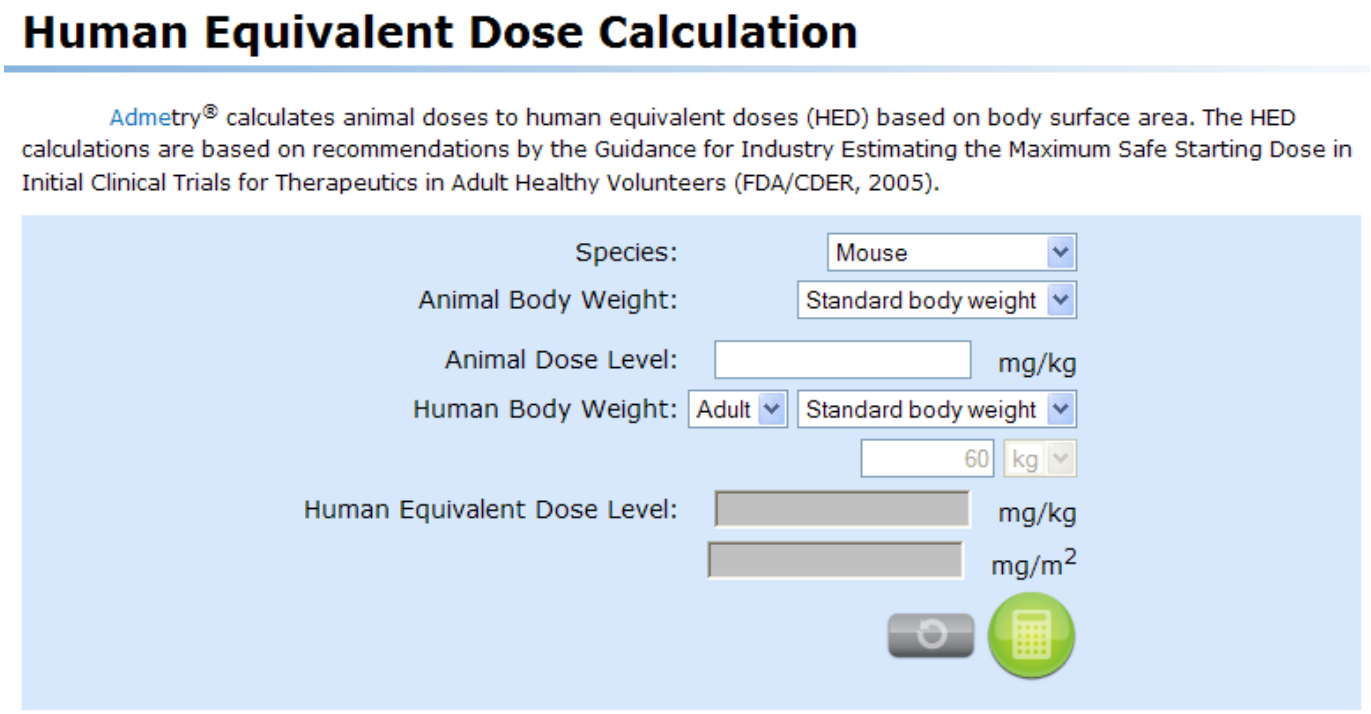


This tool converts animal doses to human equivalent doses (HED) based on body surface area. The HED calculations are based on recommendations by the Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers (FDA/CDER, 2005).

Human Equivalent Dose Calculation 5

5.2 Using Human Equivalent Dose Calculation

- Specify the species from the "Species" dropdown menu
- Input the Animal Body Weight manually by selecting "Standard body weight" or "Specified body weight" and enter the weight manually
- Enter the Animal Dose Level in mg/kg
- Select Adult or Child and specify the Human Body Weight
- Click  to project human equivalent dose levels



Symbol Definitions 6

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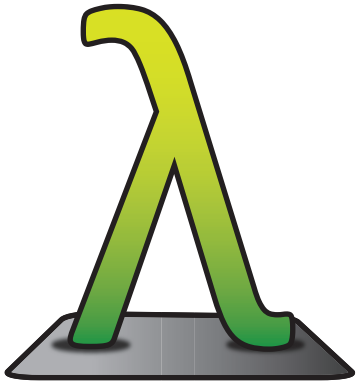
6.1 About Symbol Definitions

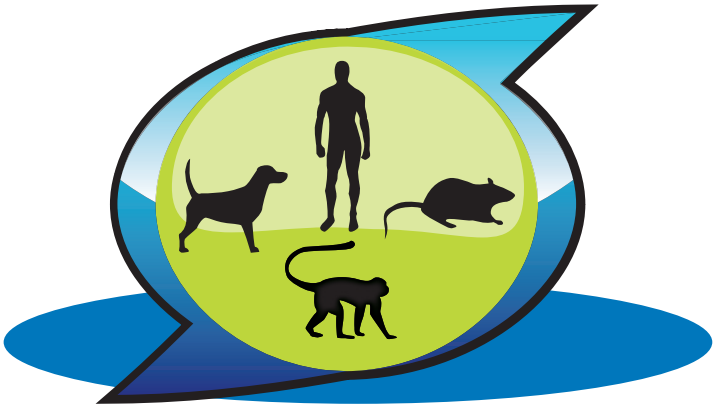


Common pharmacokinetic and toxicokinetic symbols are explained.

Symbol	Definition
AUC_{0-t}:	Area under the plasma rug concentration-time curve from time 0 to time t
AUC_{∞}:	Area under the plasma rug concentration-time curve from time 0 to time infinity
$AUMC_{0-t}$:	Total area under the first moment time curve from time 0 to time t
$AUMC_{\infty}$:	Total area under the first moment time curve from time 0 to time infinity
C_0:	Initial plasma concentration
$C_{ss,\ avg}$:	Average drug concentration in plasma at steady state
C_{max}:	Highest drug concentration observed in plasma following administration of IV or oral dose
$C_{ss,\ max}$:	Maximum drug concentration in plasma at steady state. $C_{ss,\ min} = F^* D_L / V (1 - e^{-\lambda\tau})$
$C_{ss,\ min}$:	Minimum drug concentration in plasma at steady state. $C_{ss,\ min} = F^* D_L{}^* e^{-\lambda\tau} / V (1 - e^{-\lambda\tau})$
CL:	Total systemic clearance of drug from plasma
CL_{ss}:	Total systemic clearance of drug from plasma at steady state. $CL_{ss} = Dose / AUC_{0-\tau}$

Allometry 7

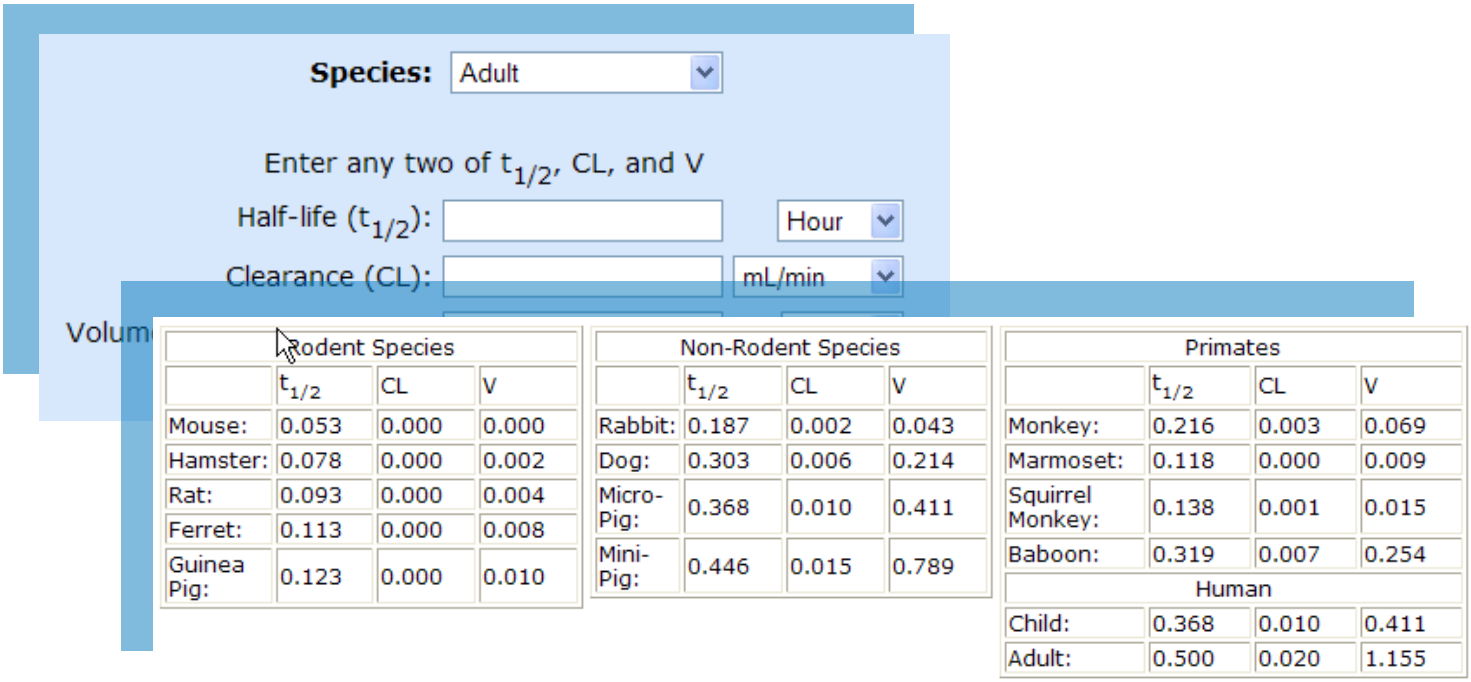
7.1 About Allometry



Allometry is used to predict PK parameters across different species.

7.2 Using Allometry

- Specify the species from the "Species" dropdown menu
- Enter any 2 of either half life, clearance, or volume of distribution
- Click "Calculate" to generate PK parameters for all other animal species

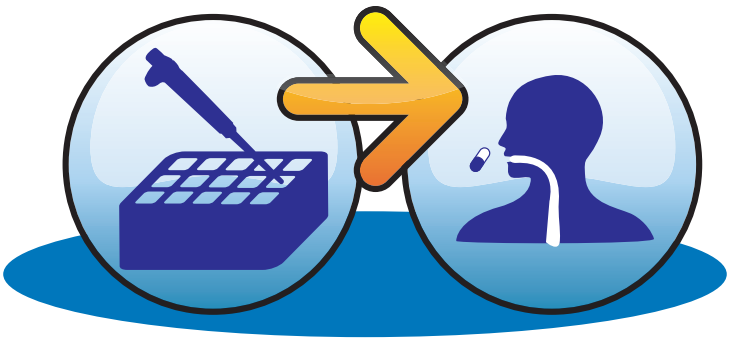


Rodent Species	$t_{1/2}$	CL	V
Mouse:	0.053	0.000	0.000
Hamster:	0.078	0.000	0.002
Rat:	0.093	0.000	0.004
Ferret:	0.113	0.000	0.008
Guinea Pig:	0.123	0.000	0.010

Non-Rodent Species	$t_{1/2}$	CL	V
Rabbit:	0.187	0.002	0.043
Dog:	0.303	0.006	0.214
Micro-Pig:	0.368	0.010	0.411
Mini-Pig:	0.446	0.015	0.789

Primates	$t_{1/2}$	CL	V
Monkey:	0.216	0.003	0.069
Marmoset:	0.118	0.000	0.009
Squirrel Monkey:	0.138	0.001	0.015
Baboon:	0.319	0.007	0.254
Human			
Child:	0.368	0.010	0.411
Adult:	0.500	0.020	1.155

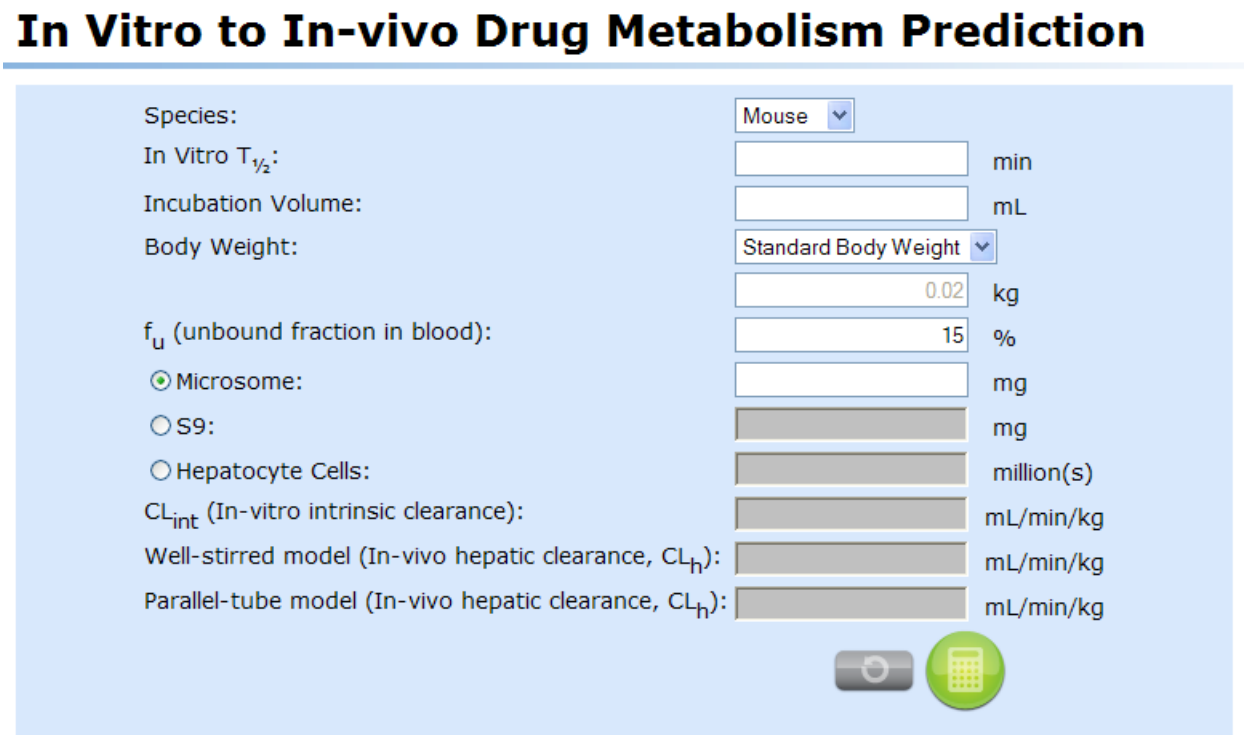
8.1 About In Vitro to In Vivo Drug Metabolism Prediction



This tool is used to predict in vivo clearance values for a species based on well-stirred and parallel-tube models.

8.2 Using In Vitro to In Vivo Drug Metabolism Prediction

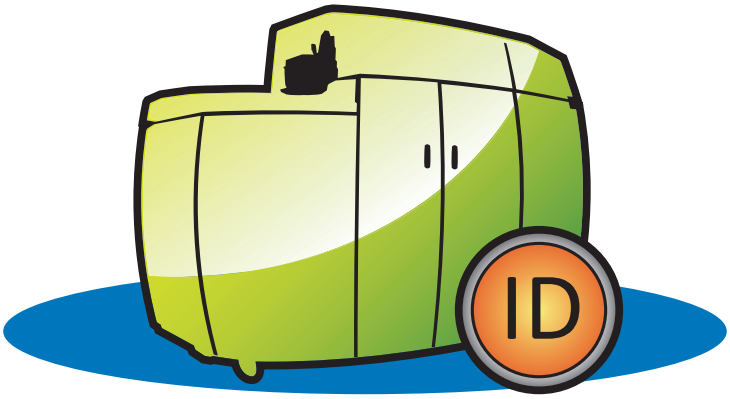
- Specify the species from the Species dropdown menu
- Enter in vitro half life, $t_{1/2}$ (min) and incubation volume (mL)
- Input the Animal Body Weight manually by selecting "standard body weight" or "specified body weight" and enter the weight manually
- Specify f_u (unbound fraction in blood)
- Enter the amount (mg) of microsomes, S9, or number of hepatic cells used
- Click "Calculate" to predict in vivo clearance values



Metabolite ID 9

Nextcea

9.1 About Metabolite ID



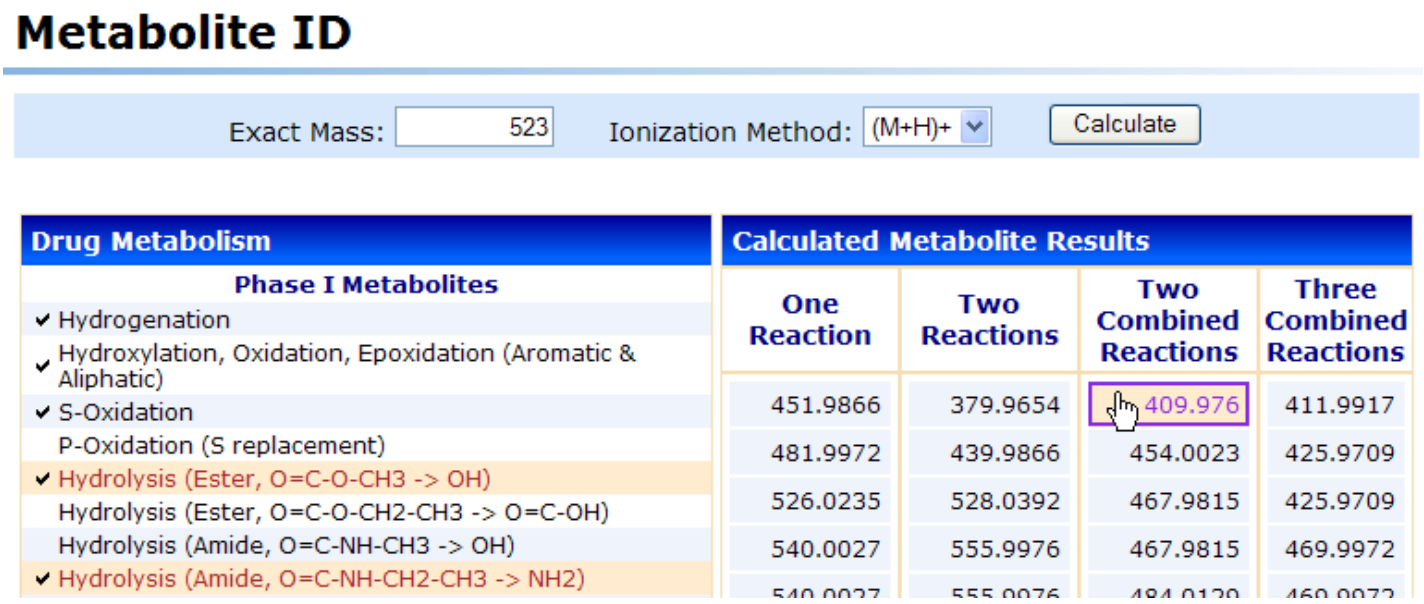
Metabolite ID is used to quickly generate all possible metabolites to identify when looking for Phase I and Phase II metabolites.

Metabolite ID 9

9.2 Using Metabolite ID

- Enter the Exact Mass of the parent compound
- Select either positive or negative ionization method: $(M+H)^+$ or $(M-H)^-$
- Check any number of Phase I and/or Phase II metabolisms based on the structure of the drug candidate if possible
- Click  to generate a list of possible metabolite ion values

Note: Scroll over the metabolite ion values to see the corresponding metabolic reactions.



Drug-Drug Interactions 10

Nextcea

10.1 About Drug-Drug Interactions

Drug-drug interaction is a quick reference for in vitro and in vivo drug-drug interaction study designs.

Drug-Drug Interactions 10

10.2 Using Drug-Drug Interactions

DDI Table

- Shows FDA preferred substrates, inhibitors, and inducers of the major CYP450 isoforms
- Scroll over any compound to see the metabolic reaction, chemical structure, formula, and exact mass

Drug Drug Interaction

DDI Table | In Vitro Table | In Vivo Table

Drug-Drug Interaction			
CYP	Substrate	Inhibitor	Inducer
1A2	Phenacetin	Furafylline	Omeprazole
2A6	Coumarin	Tranylcypromine	Dexamethasone
3A4/5	Midazolam Testoerone	Ketoconazole	Rifampin
2B6	Bupropion	Ticlopidine	Phenobarbital
2C8	Amodiaquine	Quercetin	Rifampin
2C9	Tolbutamide	Sulfaphenazole	Rifampin
2C19	S-mephenytoin	Omeprazole	Rifampin
2D6	Dextromethorphan	Quinidine	Dexamethasone
2E1	Chlorzoxazone	Diethyldithiocarbamate	Isoniazid

Drug-Drug Interactions 10

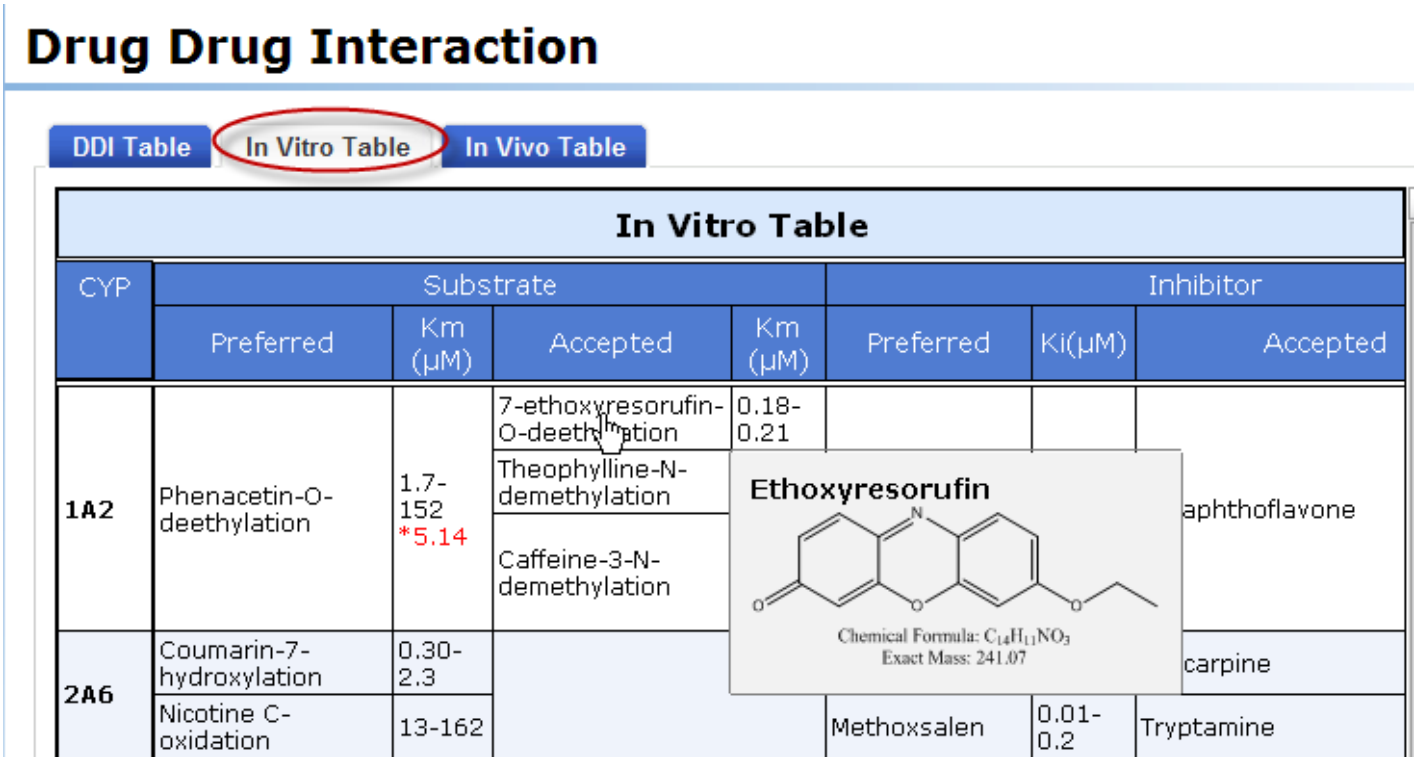
Nextcea

In Vitro Table Table

- Shows FDA preferred and accepted substrates, inhibitors, and inducers of the major CYP450 isoforms for in vitro studies

Note: Based on "Guidance to the Industry" documents, using the "preferred" list of substrates, inhibitors, and inducers is strongly encouraged, however the FDA will accept data generated using compounds in the "accepted" list.

- Scroll over any compound to see the metabolic reaction, chemical structure, formula, and exact mass



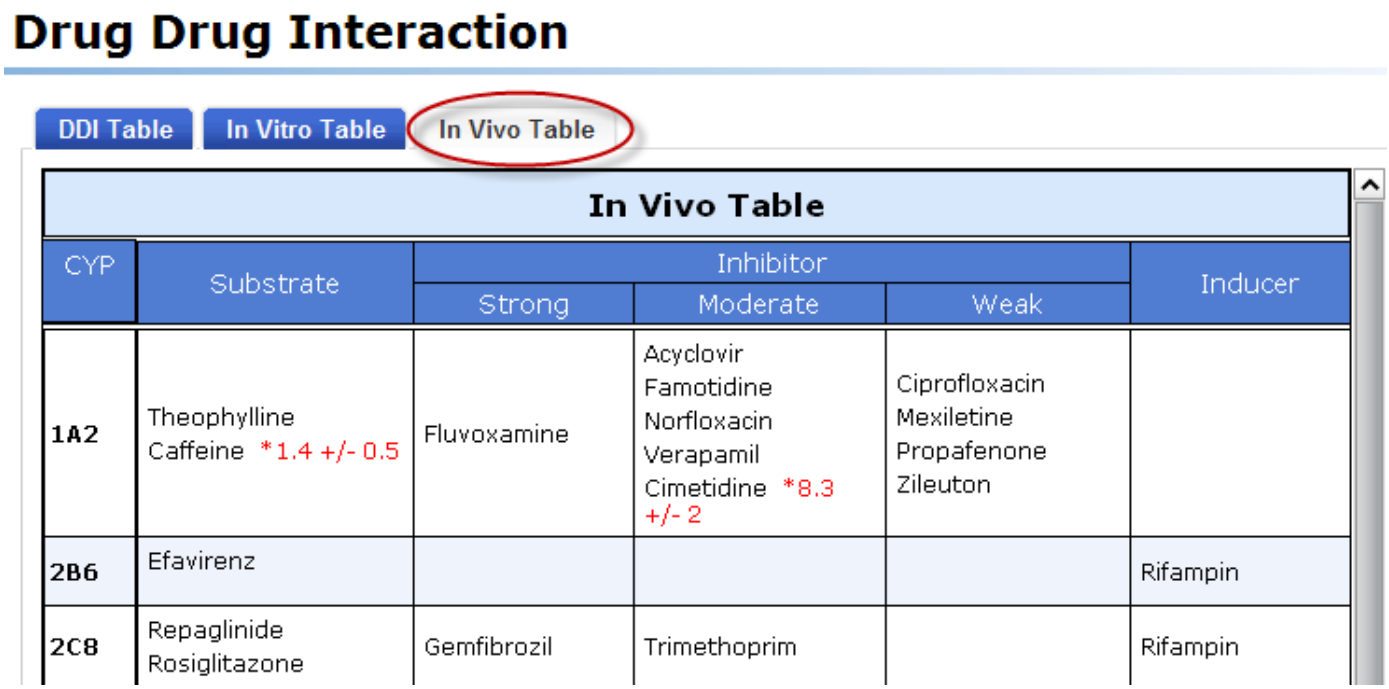
Drug-Drug Interactions 10

In Vivo Table Table

- Shows FDA preferred and accepted substrates, inhibitors, and inducers of the major CYP450 isoforms for in vivo studies

Note: Based on "Guidance to the Industry" documents, using the "preferred" list of substrates, inhibitors, and inducers is strongly encouraged, however the FDA will accept data generated using compounds in the "accepted" list.

- Scroll over any compound to see metabolism reaction, chemical structure, formula, and exact mass

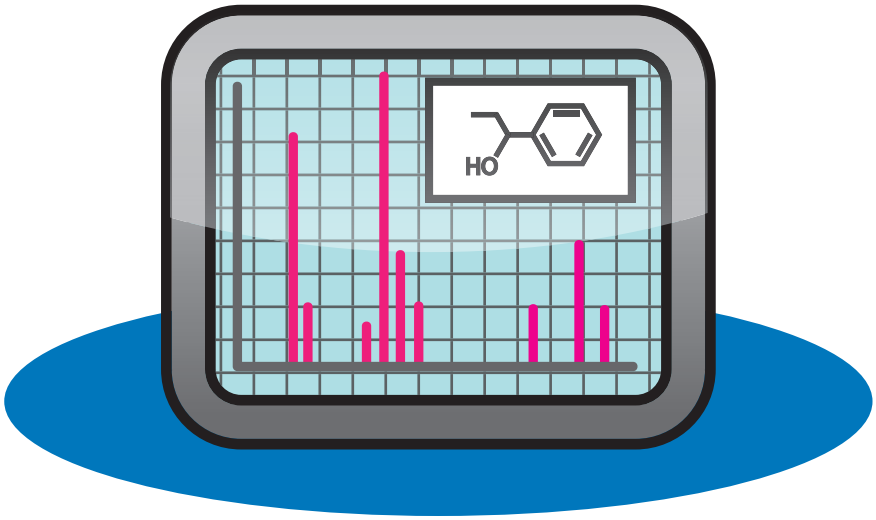


In Vivo Table

CYP	Substrate	Inhibitor			Inducer
		Strong	Moderate	Weak	
1A2	Theophylline Caffeine *1.4 +/- 0.5	Fluvoxamine	Acyclovir Famotidine Norfloxacin Verapamil Cimetidine *8.3 +/- 2	Ciprofloxacin Mexiletine Propafenone Zileuton	
2B6	Efavirenz				Rifampin
2C8	Repaglinide Rosiglitazone	Gemfibrozil	Trimethoprim		Rifampin

Drug Metabolite Scan 11

11.1 About Drug Metabolite Scan



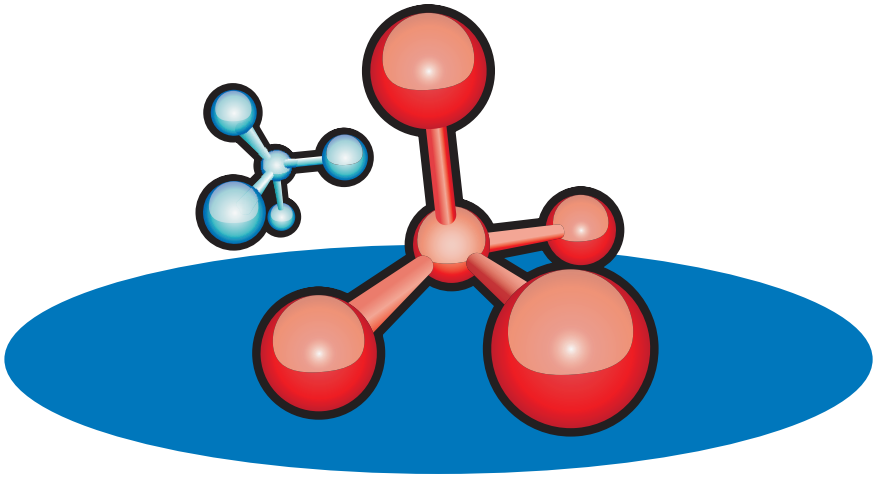
Drug Metabolite Scan is a utility to help automate the drug metabolite identification process.

Note: Additional software license is required.

A converted .wiff file from Analyst (QSTAR LC/MS/MS) to a specify data format is required to use this function.

DDI Non-competitive/Competitive 12

12.1 About DDI Non-competitive/Competitive



Non-Competitive/Competitive Drug-Drug Interaction calculates drug-drug interactions using Michaelis-Menten-Henri, Lineweaver-Burk, Hanes-Woolf, and Eadie-Hofstee models.

DDI Non-competitive/Competitive 12

12.2 Using DDI Non-competitive/Competitive

Enter background study design information:

- Study Title
- Compound Name
- Species
- Strain
- CYP450 Enzymes, Incubation Time, and Inhibitor Concentration

DDI Non-competitive/Competitive 12

- Copy drug-drug interaction data from Excel

	A	B	C	D	E
1		V (Velocity), umol/min			
2	[S], uM	No inhibition	Inhibition		
3	3	10.4	4.1		
4	5	14.5	6.4		
5	10	22.5	11.3		
6	30	33.8	22.6		
7	90	40.5	33.8		
8					
9					
10	Inhibitor Conc = 2mM = 2000 uM				
11					
12					
13					

In Excel

- In Admetry®, click "Paste Data"

DDI Non-competitive/Competitive

Study Title: NEX008

Compound (Drug Candidate) Names: NEX008

Incubation Time: 30 min

Inhibitor Concentration: 2.5 ng/mL

Species: Mouse Strain/Type: CD-1

CYP P450 Enzymes: Microsomes

Paste Data | Clear Data

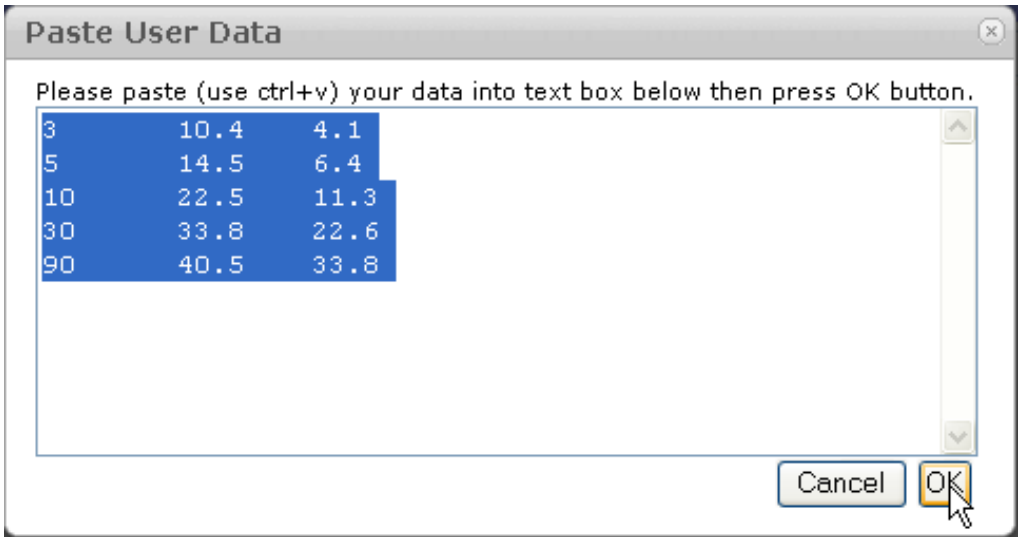
	Substrate Conc ng/mL	Product Conc Without Inhibitor	Product Conc With Inhibitor
1			

DDI Non-competitive/Competitive 12 Nextcea

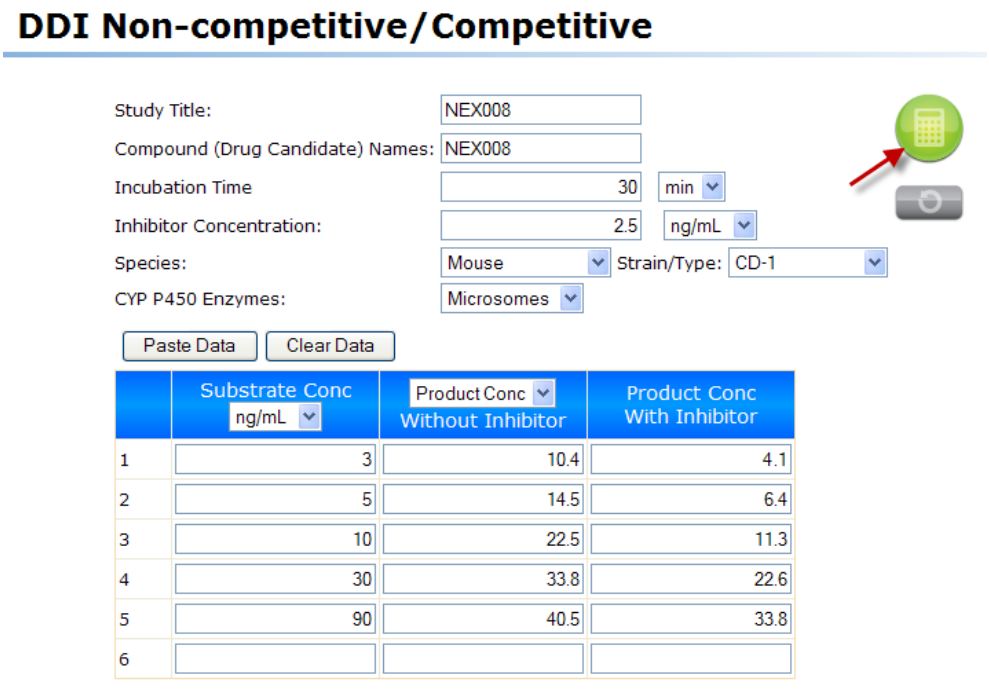
Note:
Make sure data is copied from columns in the following order from left to right:

Substrate concentration → Velocity without inhibition → Velocity with inhibition

- Click "OK"



- Click "Calculate" to calculate to graph results.

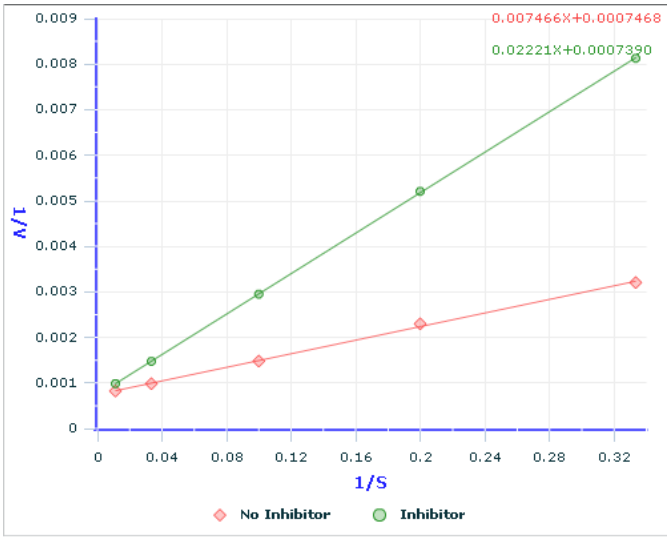


	Substrate Conc ng/mL	Product Conc Without Inhibitor	Product Conc With Inhibitor
1	3	10.4	4.1
2	5	14.5	6.4
3	10	22.5	11.3
4	30	33.8	22.6
5	90	40.5	33.8
6			

DDI Non-competitive/Competitive 12

- Select either “Non-Competitive” or “Competitive” inhibition based on the resulting graph

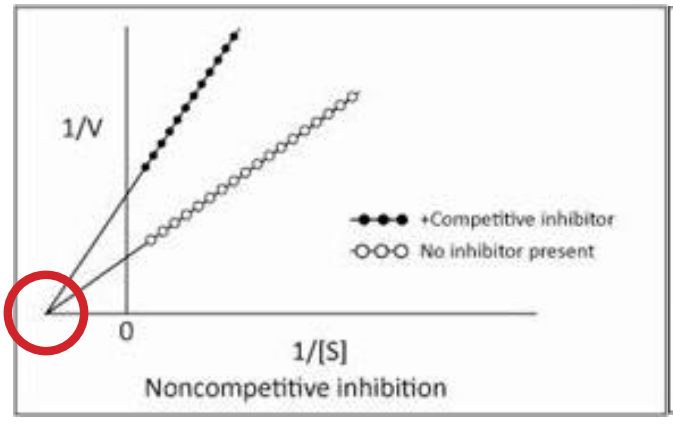
Note: Non-Competitive Inhibition graphs intersect on the Y-axis (1/V)
Competitive Inhibitions graphs intersect on the X-axis (1/[S])



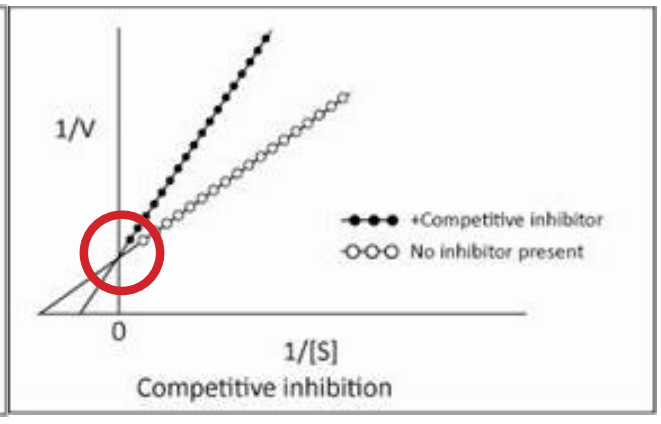
Non-Competitive or Competitive Inhibition:

Noncompetitive Inhibition | Competitive Inhibition

Non-Competitive

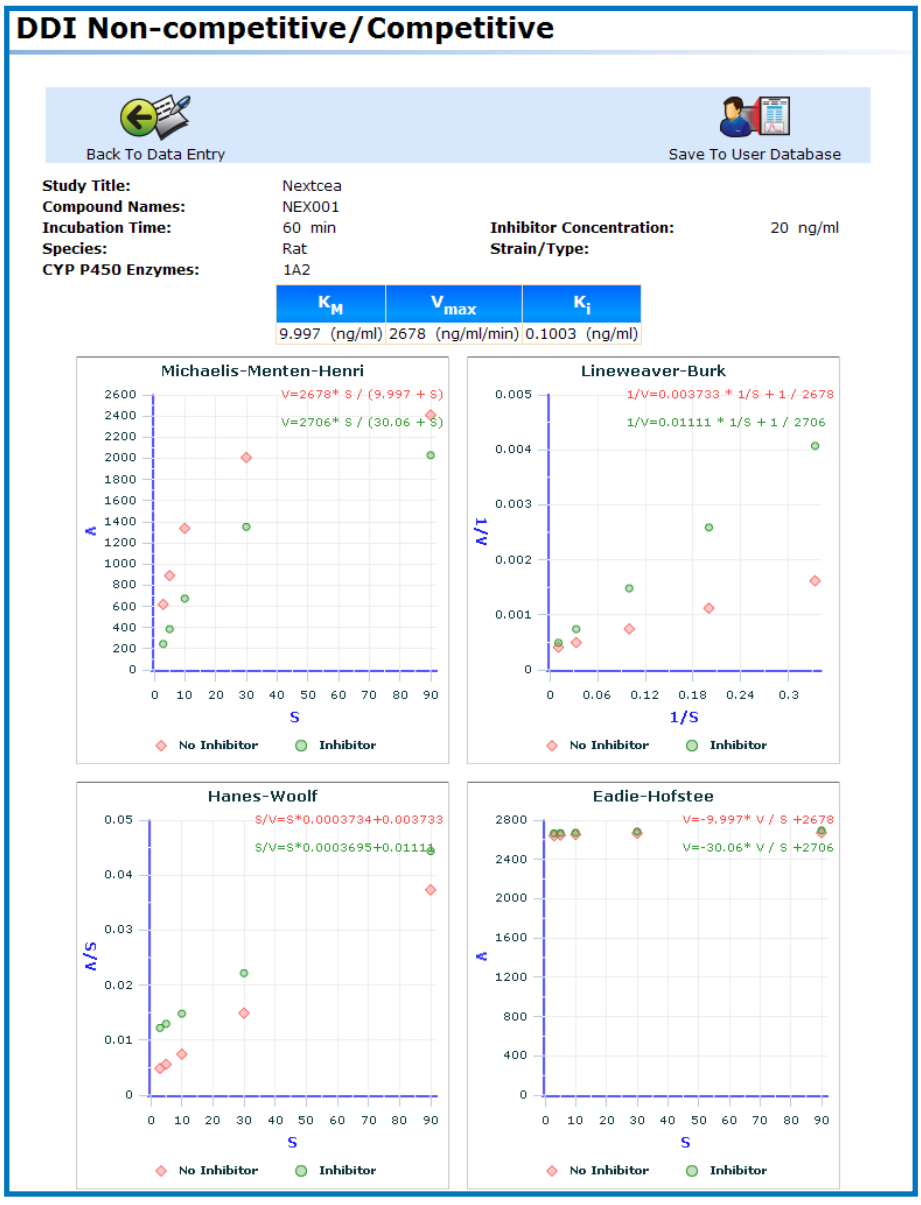


Competitive



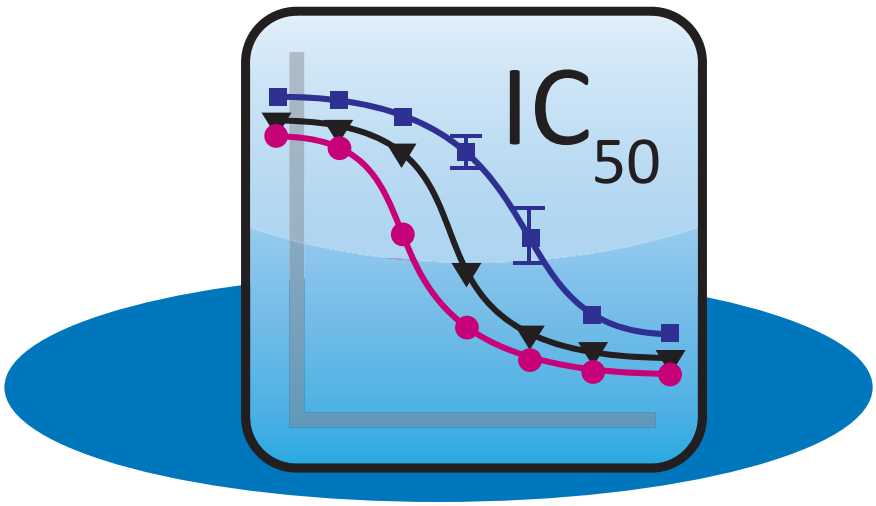
DDI Non-competitive/Competitive 12 Nextcea

- The results are graphed using Michaelis-Menten-Henri, Lineweaver-Burk, Hanes-Woolf, and Eadie-Hofstee equations
- K_m, V_{max}, and K_i are calculated
- Click "Save to User Database" to save
- Click "Back to Data Entry" to go back to background study design information

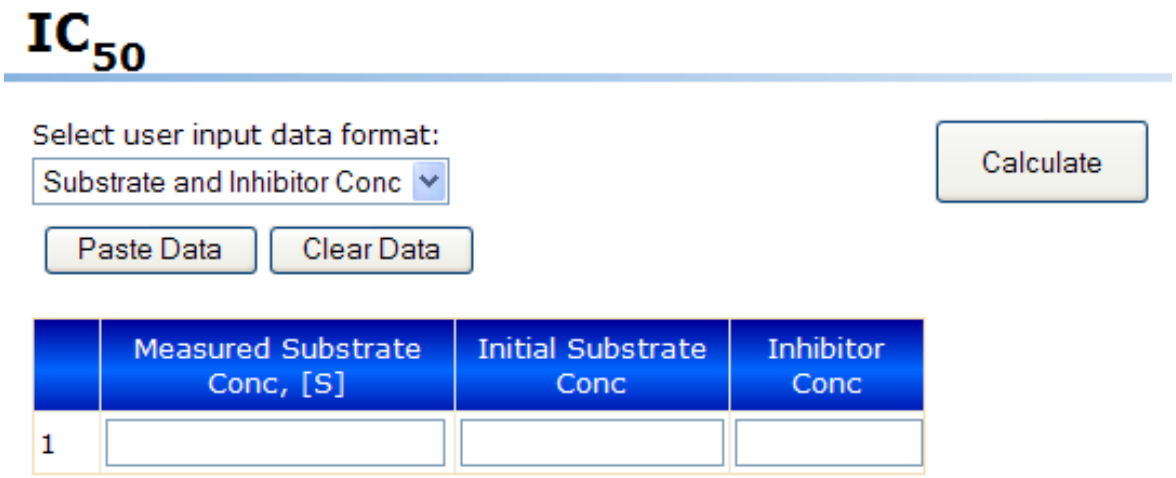


IC_{50} Determination 13

13.1 About IC_{50} Determination



This function calculates of the effectiveness of a compound in inhibiting biological function. It calculates the half maximal inhibitory concentration (IC_{50}) from submitted substrate concentration information.



IC_{50} Determination 13

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13.2 Using IC_{50} Determination

- Select either "% of P450 Inhibition" or "Substrate and Inhibitor Conc" data input
- Manually enter or paste in data from Excel

- Click calculation button 
- View results, IC_{50} is calculated

IC_{50}

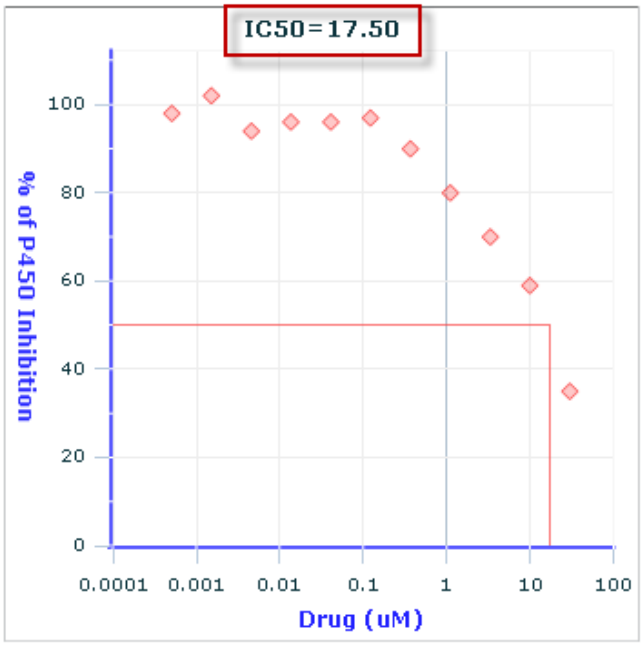
Select user input data format:

% of P450 Inhibition

Paste Data | Clear Data

	% of P450 Inhibition	Inhibitor Conc
1	98	0.000508
2	102	0.00152
3	94	0.00457
4	96	0.0137
5	96	0.0412
6	97	0.123
7	90	0.37
8	80	1.11
9	70	3.33
10	59	10
11	35	30
12		

Calculate



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