

# Admetry<sup>®</sup> User Manual

Pharmacokinetic and Drug Metabolism Data Analysis for Everyone



# Forward

Admetry® User Manual  
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# About Admetry®




**A**dmetry® 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.



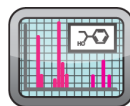
## In Vivo Clearance Prediction

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.



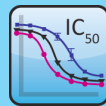
## Drug Metabolite Scan

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.



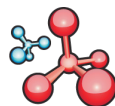
## IC50 Determination

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.

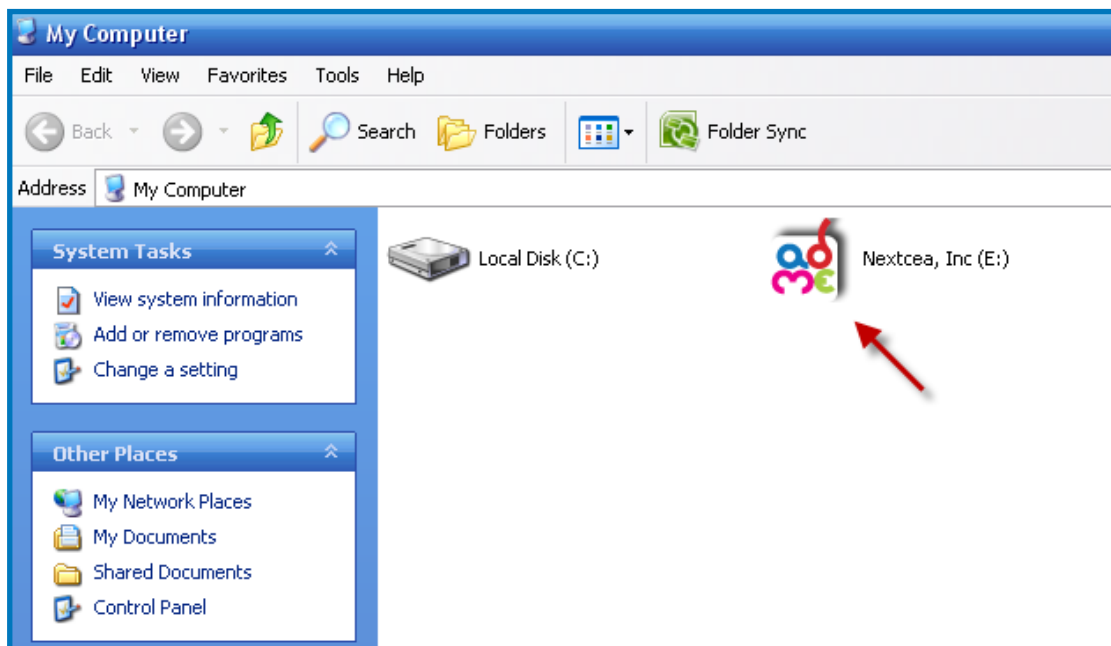
# Getting Started 2

## 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

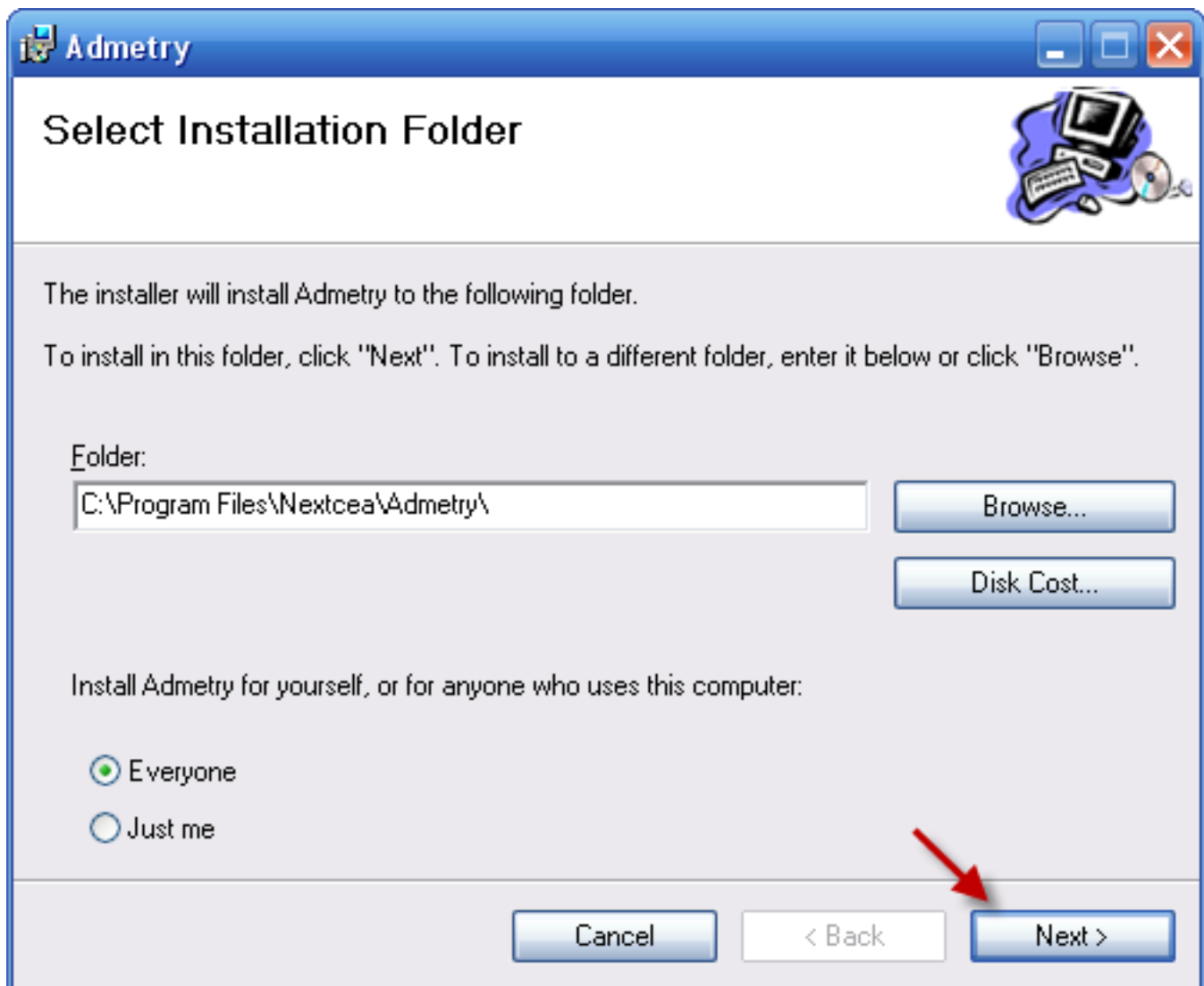
- Click "Next"



# 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”



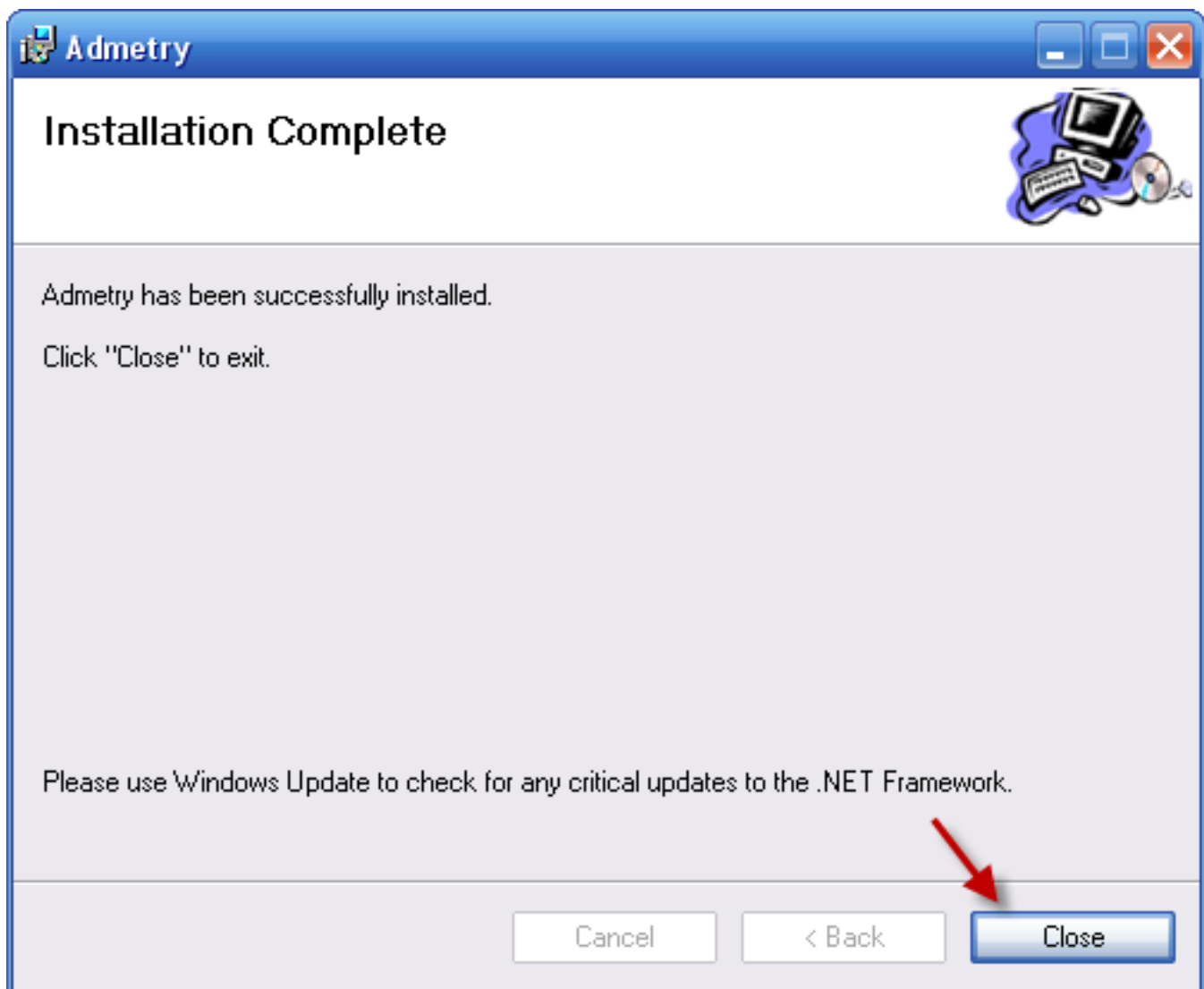


# Getting Started 2

## 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



# Getting Started 2



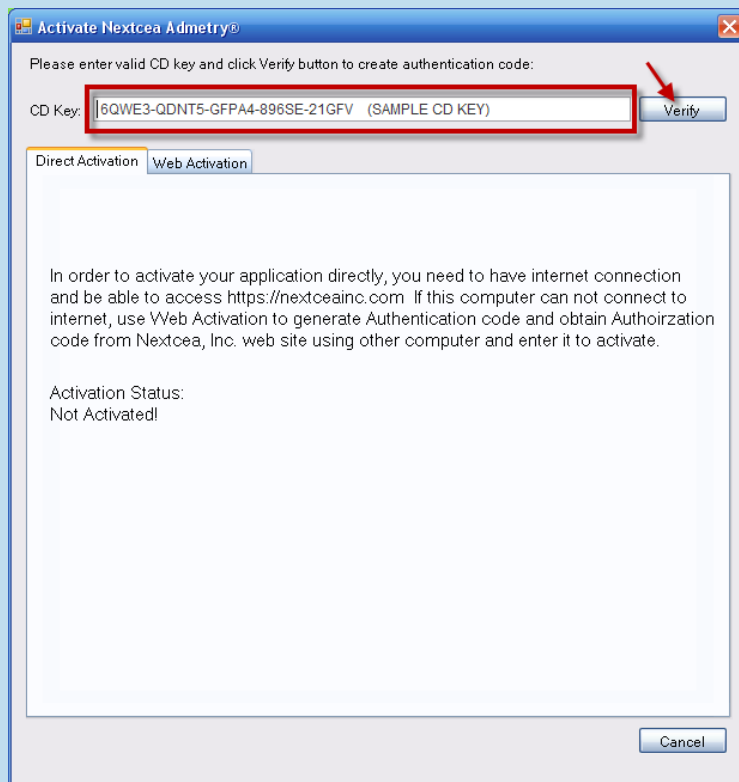
## Activating Admetry®

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"



Activate Nextcea Admetry®

Please enter valid CD key and click Verify button to create authentication code:

CD Key:

Direct Activation | Web Activation

In order to activate your application directly, you need to have internet connection and be able to access <https://nextceainc.com>. If this computer can not connect to internet, use Web Activation to generate Authentication code and obtain Authorization code from Nextcea, Inc. web site using other computer and enter it to activate.

Activation Status:  
Not Activated!

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

# Getting Started 2



- 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](mailto:Admetry@nextcea.com) should you experience any problems during activation.

# Getting Started 2

## 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 “Activate Admetry”.

# Getting Started 2



Please enter valid CD key and click Verify button to create authentication code:

1

Direct Activation **Web Activation**

Authentication Code: 2

```
04wSDFfsfw3w3223490vmdlvj3490fjw
eDK3r-f9asdfjdsfqqeb3#(3fr09jc;df4g
tbvdcvxcvbCEef=
```

Obtain you authorization code by enter your authentication code to web page:  
<https://nextceainc.com/PkTk/PublicContent/AuthorizeAdmetry.aspx>

Authorization Code: 6

Activation Status:  
Not Activated! 7

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

# Getting Started 2

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

The screenshot displays the Nextcea website interface. At the top, there is a navigation bar with the Nextcea logo and links for "About Nextcea", "Home", and "Contact Us". Below this, the website is divided into three main sections: "Biomarker Services", "DMPK/ADME", and "Products". Each section contains several sub-categories with corresponding icons: "Drug Efficacy", "Drug Safety", "Drug-Induced Phospholipidosis", "New Drug Indications", "Metabolite ID", "Drug Drug Interactions", "ADME Bioinformatics Admetry®", and "Synthetic PL Biomarker".

In the center of the page, there is a form titled "Please enter your Authentication Code:". The input field contains a long alphanumeric string: `dd&84s42sp23-_%^12=3=2301~_pno57aqh48vhk1-vma-c4nh&6%7fam&50#4s42sp23-_57aqh48vhk19204Biad`. A red arrow points to a "Submit" button below the input field.

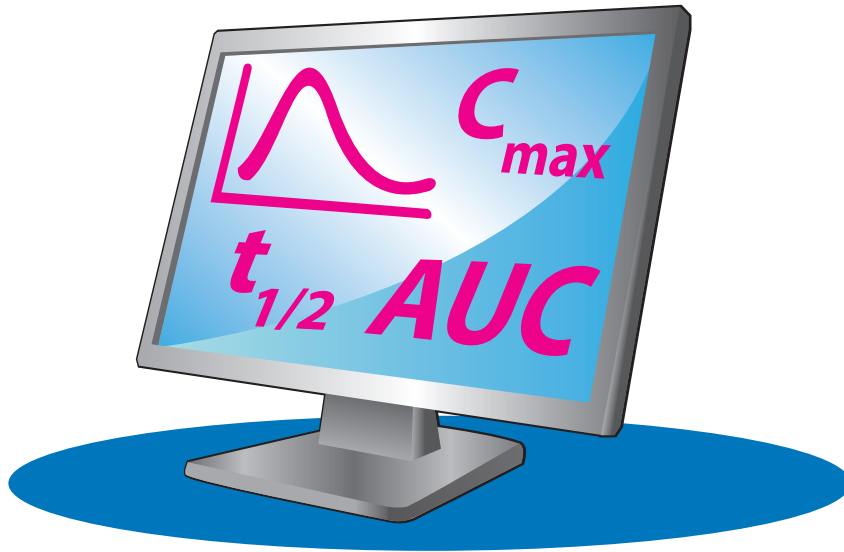
Below the "Submit" button, the text "This is your Authorization Code:" is displayed. The input field now contains a different alphanumeric string: `95ad&84sa1ab2sp23-_%^12=3=2301~_ncbno5795qh48vhk1-vma-c4nh&6%7fam&50#4s42sp23-_577aqh48vhk179204Biadaa2457`. A red box highlights this string, and a red arrow points to it with the text "Copy Authorization Code".

A blue box on the right side of the page is labeled "Nextcea 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](mailto:Admetry@nextcea.com) should you experience any problems during this step.

## 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<sup>2</sup>” in addition to “per kg”.

Units <i>without</i> species selected		Units <i>with</i> species selected	
V <sub>z</sub>	52.8 mL/kg	V <sub>z</sub>	52.8 mL/kg
V <sub>ss</sub>	36.6 mL/kg	V <sub>ss</sub>	158 mL/m <sup>2</sup>
CL	5.91 mL/hour/kg	CL	17.7 mL/hour/m <sup>2</sup>

- 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

## Pharmacokinetic And Toxicokinetic Analysis

### Tutorial PK/TK Data

Study Protocol/Title:

Species:  Strain/Type:

Body Weight:

Dose By:  Gender:

Single or Multiple Administration:





### 3.3 Enter route of administration and dosing level

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

The image shows two side-by-side panels for selecting the route of administration. The left panel is titled "Select checkbox for route of administration" and has the "IV Dose" checkbox checked. Below it, under "(Option One)", is a checkbox for "Calculate steady state after repeat dose" which is unchecked. There are input fields for "Dose Interval" (set to 0) and "Dose Time" (set to 0), both with "Minute" dropdown menus. Under "(Option Two)", there is a "Protein Binding" input field set to 0%. At the bottom, a "Dose" input field is highlighted with a red box, containing the value "2.5" and a "mg" dropdown menu, followed by a "/kg" label. The right panel is titled "Select checkbox for route of administration" and has the "Extravascular Dose (Oral, Tropical, Inhalation, Percutaneous, Rectal, Transdermal and Subcutaneous)" checkbox unchecked. It has the same "Calculate steady state after repeat dose" checkbox (unchecked) and "Dose Interval" and "Dose Time" fields (both set to 0). Under "(Option Two)", there are "Bioavailability" (set to 1) and "Protein Binding" (set to 0%) input fields. At the bottom, there is a "Dose" input field with a "mg" dropdown menu and a "/kg" label. Red arrows point from the text above to the "IV Dose" and "Extravascular Dose" checkboxes respectively.

### 3.4 Calculate steady state (optional)

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

The image shows a close-up of the "(Option One)" section of the software interface. The checkbox "Calculate steady state after repeat dose" is checked. Below it, the "Dose Interval" is set to 24 with a "Hour" dropdown menu, and the "Dose Time" is set to 8 with a "Hour" dropdown menu.

## 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 (%)

(Option Two)

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

## 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"

The screenshot shows the Admetry software interface. At the top, there are two buttons: "Paste Bioanalytical Data" and "Clear All". Below these buttons is a data entry form with two columns. The first column is labeled "Time" with a dropdown menu set to "hour". The second column is labeled "Conc" with a dropdown menu set to "ng/mL". Below the columns, there is a row with the number "001" in a small box and two empty input fields.

- Identify the columns and click "OK"
- (Note: As a default, Column 1 is set to "Time" and Column 2 is set to "Conc")

The screenshot shows the "Paste Bioanalytical Data" dialog box. It contains the following text: "Please select your paste data format first, then click 'OK' to process pasted data." Below this text are four columns labeled "Column 1", "Column 2", "Column 3", and "Column 4". Column 1 has a dropdown menu set to "Time", and Column 2 has a dropdown menu set to "Conc". Below the columns is a list of data points: 0.017 48445.0, 0.083 40970.0, 0.250 25045.0, 0.500 23518.0, 0.750 17791.0, 1.000 21477.0, 2.000 12430.0, 3.000 13184.0, 4.000 10408.0, 6.000 8052.0. At the bottom right of the dialog box are "Cancel" and "OK" buttons. A red arrow points to the "OK" button.

## 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



Back To Data Entry



Save To User Database



Export To Excel

Significant Digit

## 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.

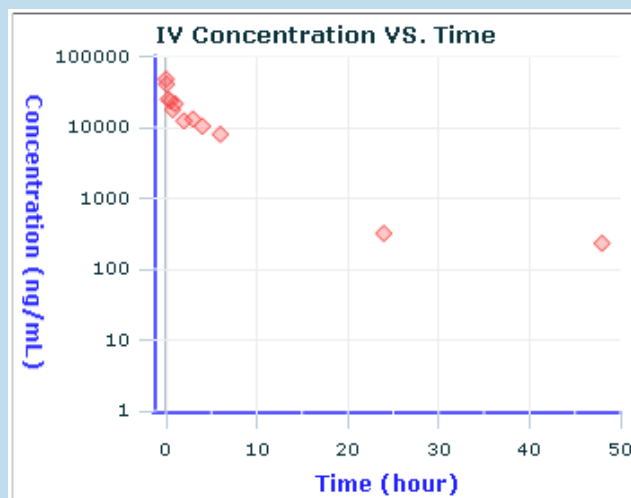
## 3.12 Single-dose results

## 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
$AUC_{\infty}$	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 <sup>2</sup>
$V_{ss}$	183	mL/kg
	549	mL/m <sup>2</sup>
CL	29.5	mL/hour/kg
	88.4	mL/hour/m <sup>2</sup>
$C_{max}/Dose$	9.69e+3	(ng/mL)/(mg/kg)
	2.91e+4	(ng/mL)/(mg/m <sup>2</sup> )

## Drug concentration vs. time graph

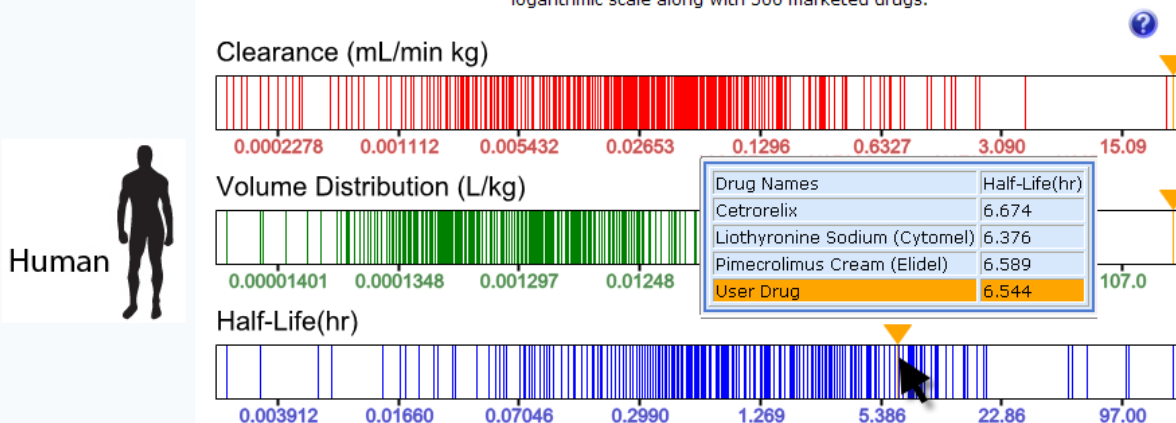


## PK/TK Allometric Visualizer

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.

## PK/TK Allometric Visualizer

This visualizer uses allometric calculations to predict PK/TK parameters from human models then plot them on a logarithmic scale along with 500 marketed drugs.



## 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.

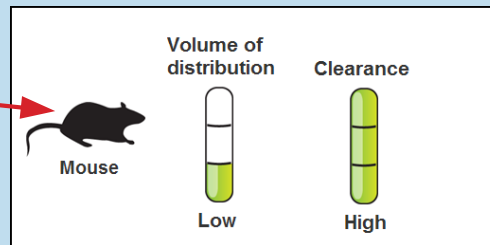
### Volume of Distribution

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

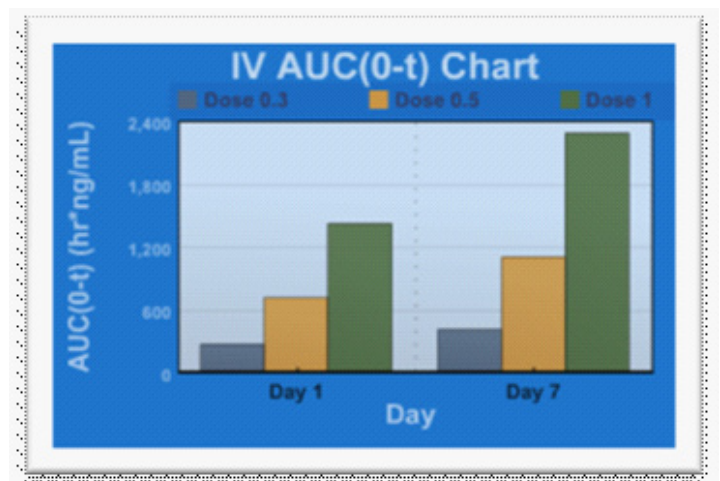
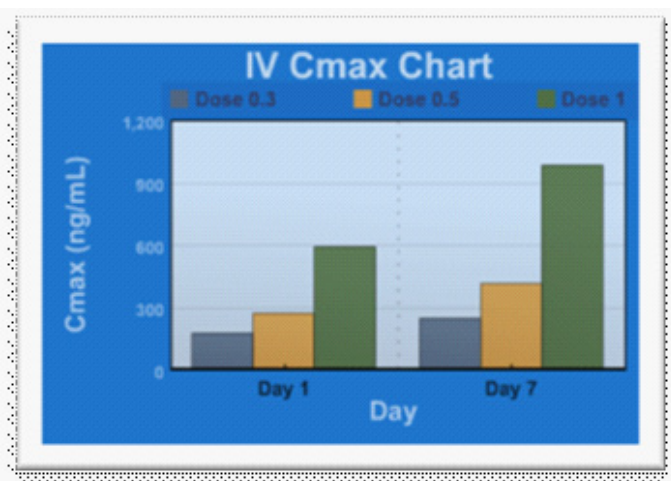
### Clearance (Hepatic + Renal)

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

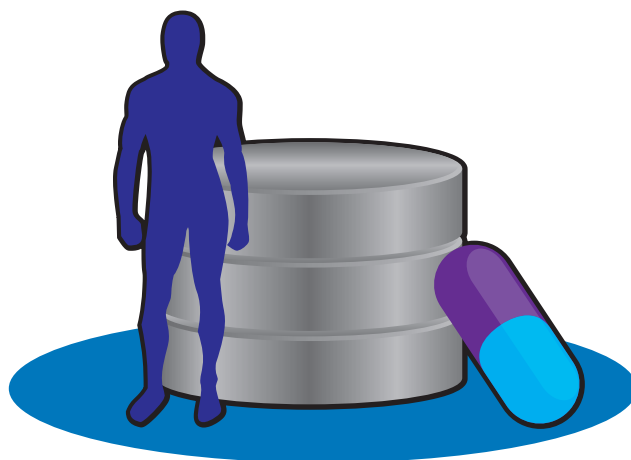
Parameter Name	Value	Unit
Dose Level	1.00	mg/kg
Protein Binding	0.00%	
$C_0$	0.00	ng/mL
$C_{max}$	4.84e+4	ng/mL
$t_{max}$	0.0170	hour

#### 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



## 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):  to

Volume of Distribution (L/kg):  to

Clearance (mL/min\*kg):  to

---

Or search by

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

## 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

### Clinical Pharmacology Database

Half Life (hr):  to

Volume of Distribution (L/kg):  to

Clearance (mL/min\*kg):  to

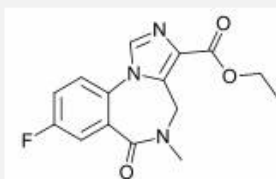
---

Or search by

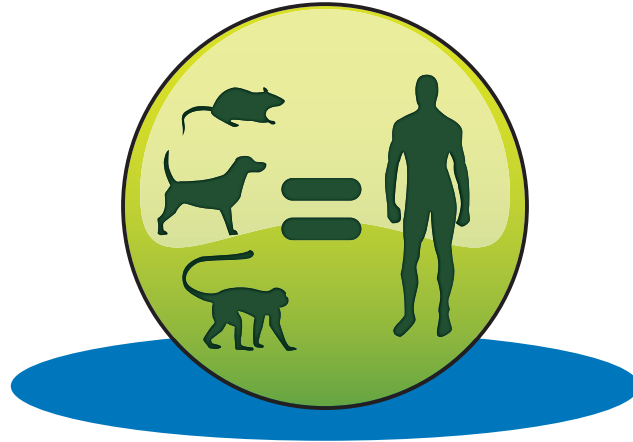
Drug	Clearance (mL/min kg)	Volume Distribution (L/kg)	Half-Life (hr)
Cocaine	32	2	0.8
Flumazenil	17	1	0.9
Glycopyrrrolate (Robinul)	30	1.4	0.5
Hydralazine	56		
Penicillamine (Cuprimine)	9.3		

#### Flumazenil

<b>Bioavailability (oral, %):</b>	20
<b>Clearance (mL/min kg):</b>	17
<b>Volume Distribution (L/kg):</b>	1
<b>Half-Life (hr):</b>	0.9
<b>Therapeutic Class:</b>	Sedative effects of benzodiazepines
<b>Chemical Formula:</b>	C <sub>15</sub> H <sub>14</sub> FN <sub>3</sub> O <sub>3</sub>
<b>Molecular Weight:</b>	303.2884



## 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

### Human Equivalent Dose Calculation

Admetry® calculates 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).

Species:  ▾

Animal Body Weight:  ▾


Animal Dose Level:  mg/kg

Human Body Weight:  ▾  ▾

▾

Human Equivalent Dose Level:  mg/kg

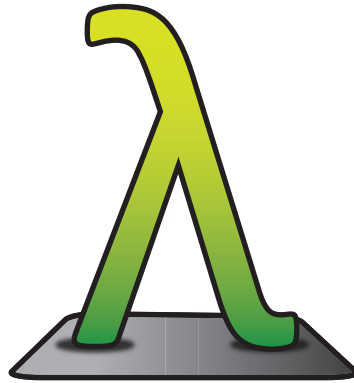
mg/m<sup>2</sup>



# Symbol Definitions

## 6

### 6.1 About Symbol Definitions



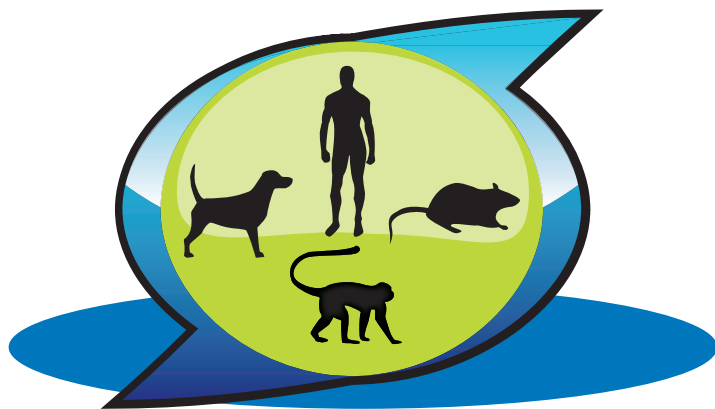
Common pharmacokinetic and toxicokinetic symbols are explained.

#### Symbol Definition

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

# 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

Species:

Enter any two of  $t_{1/2}$ , CL, and V

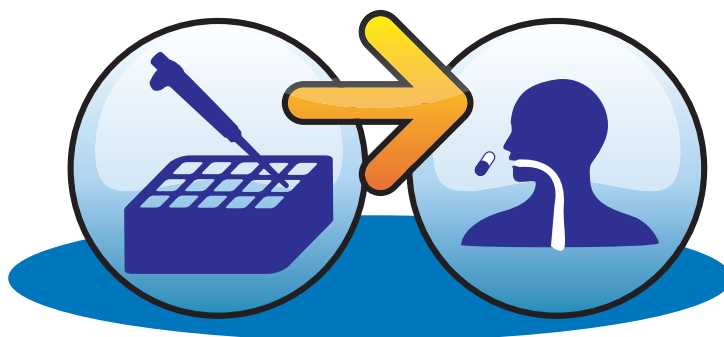
Half-life ( $t_{1/2}$ ):

Clearance (CL):

Volume

	Rodent Species			Non-Rodent Species			Primates				
	$t_{1/2}$	CL	V		$t_{1/2}$	CL	V		$t_{1/2}$	CL	V
Mouse:	0.053	0.000	0.000	Rabbit:	0.187	0.002	0.043	Monkey:	0.216	0.003	0.069
Hamster:	0.078	0.000	0.002	Dog:	0.303	0.006	0.214	Marmoset:	0.118	0.000	0.009
Rat:	0.093	0.000	0.004	Micro-Pig:	0.368	0.010	0.411	Squirrel Monkey:	0.138	0.001	0.015
Ferret:	0.113	0.000	0.008	Mini-Pig:	0.446	0.015	0.789	Baboon:	0.319	0.007	0.254
Guinea Pig:	0.123	0.000	0.010					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.

## In Vitro to In Vivo Drug Metabolism Prediction



## 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

### In Vitro to In-vivo Drug Metabolism Prediction

Species:	Mouse	
In Vitro $T_{1/2}$ :	<input type="text"/>	min
Incubation Volume:	<input type="text"/>	mL
Body Weight:	Standard Body Weight	
	<input type="text" value="0.02"/>	kg
$f_u$ (unbound fraction in blood):	<input type="text" value="15"/>	%
<input checked="" type="radio"/> Microsome:	<input type="text"/>	mg
<input type="radio"/> S9:	<input type="text"/>	mg
<input type="radio"/> Hepatocyte Cells:	<input type="text"/>	million(s)
$CL_{int}$ (In-vitro intrinsic clearance):	<input type="text"/>	mL/min/kg
Well-stirred model (In-vivo hepatic clearance, $CL_H$ ):	<input type="text"/>	mL/min/kg
Parallel-tube model (In-vivo hepatic clearance, $CL_H$ ):	<input type="text"/>	mL/min/kg



# Metabolite ID 9


## 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.

### Metabolite ID

Exact Mass:  Ionization Method:  $(M+H)^+$

Drug Metabolism	Calculated Metabolite Results			
Phase I Metabolites	One Reaction	Two Reactions	Two Combined Reactions	Three Combined Reactions
✓ Hydrogenation				
✓ Hydroxylation, Oxidation, Epoxidation (Aromatic & Aliphatic)				
✓ S-Oxidation	451.9866	379.9654	409.976	411.9917
P-Oxidation (S replacement)	481.9972	439.9866	454.0023	425.9709
✓ Hydrolysis (Ester, $O=C-O-CH_3 \rightarrow OH$ )	526.0235	528.0392	467.9815	425.9709
Hydrolysis (Ester, $O=C-O-CH_2-CH_3 \rightarrow O=C-OH$ )	540.0027	555.9976	467.9815	469.9972
Hydrolysis (Amide, $O=C-NH-CH_3 \rightarrow OH$ )	540.0027	555.9976	484.0120	460.0072
✓ Hydrolysis (Amide, $O=C-NH-CH_2-CH_3 \rightarrow NH_2$ )				

# Drug-Drug Interactions

# 10

## 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

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

# Drug-Drug Interactions

# 10



## In Vitro Table

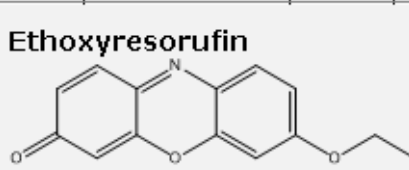
- Shows FDA preferred and accepted substrates, inhibitors, and inducers of the major CYP450 isoforms for in vitro studies

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 Interaction

DDI Table **In Vitro Table** In Vivo Table

In Vitro Table							
CYP	Substrate				Inhibitor		
	Preferred	Km (μM)	Accepted	Km (μM)	Preferred	Ki(μM)	Accepted
1A2	Phenacetin-O-deethylation	1.7-152 *5.14	7-ethoxyresorufin-O-deethylation	0.18-0.21	 <p><b>Ethoxyresorufin</b> Chemical Formula: C<sub>14</sub>H<sub>11</sub>NO<sub>3</sub> Exact Mass: 241.07</p>		aphthoflavone
			Theophylline-N-demethylation				
			Caffeine-3-N-demethylation				
2A6	Coumarin-7-hydroxylation	0.30-2.3					carpine
	Nicotine C-oxidation		13-162		Methoxsalen	0.01-0.2	Tryptamine

# Drug-Drug Interactions

# 10

## In Vivo 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

## Drug Drug Interaction

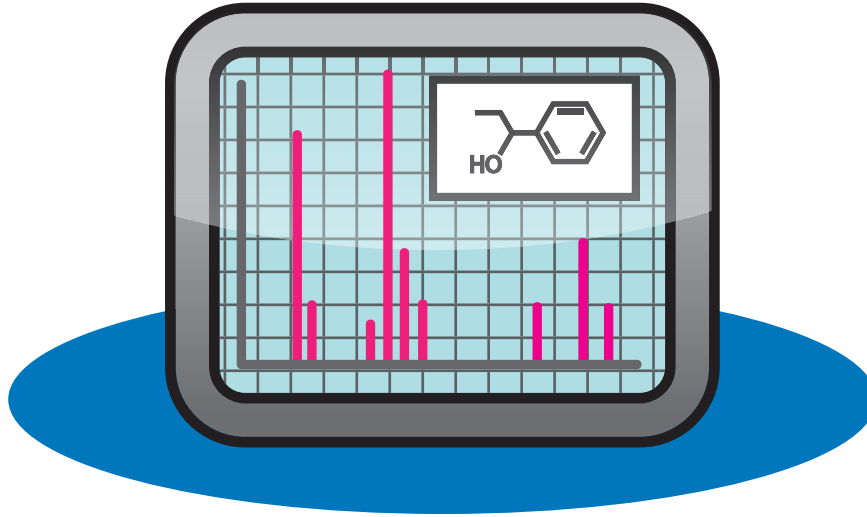
DDI Table   In Vitro Table   **In Vivo Table**

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



## 11.1 About Drug Metabolite Scan



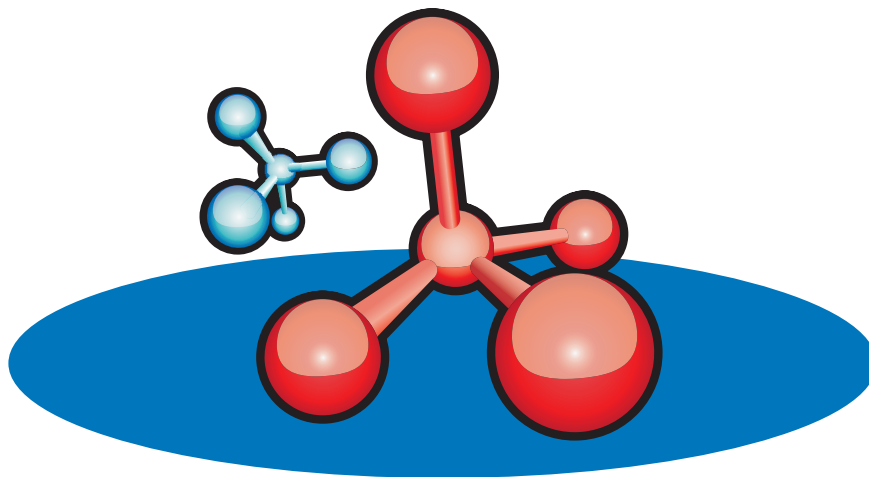
Drug Metabolite Scan is a utility to help automate the drug metabolite identification process.

*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 *N*extcea

## 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

Study Title:

Compound (Drug Candidate) Names:



Incubation Time:  min

Inhibitor Concentration:  ng/mL

Species:  Strain/Type:

CYP P450 Enzymes:

	Substrate Conc ng/mL <input type="button" value="ng/mL"/>	Product Conc <input type="button" value="Product Conc"/> Without Inhibitor	Product Conc With Inhibitor
1	<input type="text"/>	<input type="text"/>	<input type="text"/>

# 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:

Compound (Drug Candidate) Names:

Incubation Time:  min

Inhibitor Concentration:  ng/mL

Species:  Strain/Type:

CYP P450 Enzymes:

	Substrate Conc ng/mL	Product Conc Without Inhibitor	Product Conc With Inhibitor
1	<input type="text"/>	<input type="text"/>	<input type="text"/>

## DDI Non-competitive/Competitive

12 *N*extcea

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"

**Paste User Data**

Please paste (use ctrl+v) your data into text box below then press OK button.

3	10.4	4.1
5	14.5	6.4
10	22.5	11.3
30	33.8	22.6
90	40.5	33.8

Cancel OK

- Click "Calculate" to calculate to graph results.

### DDI Non-competitive/Competitive

Study Title:

Compound (Drug Candidate) Names:

Incubation Time:  min

Inhibitor Concentration:  ng/mL

Species:  Strain/Type:

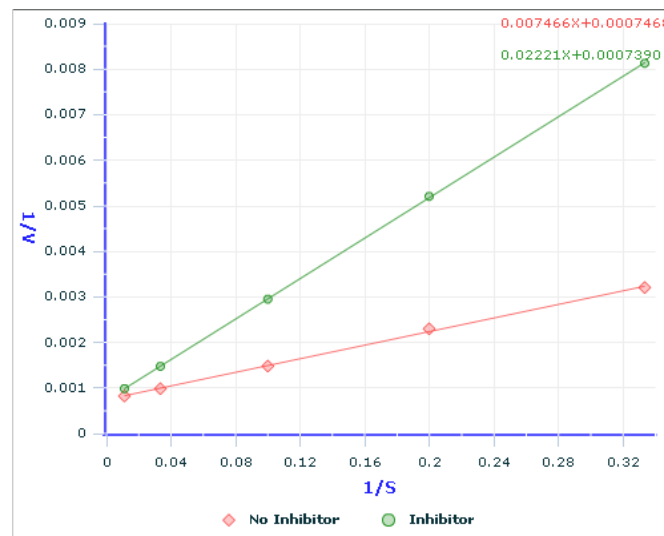
CYP P450 Enzymes:

	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])

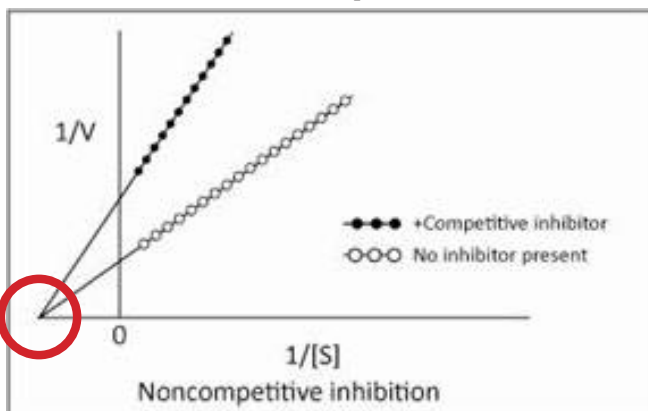


**Non-Competitive or Competitive Inhibition:**

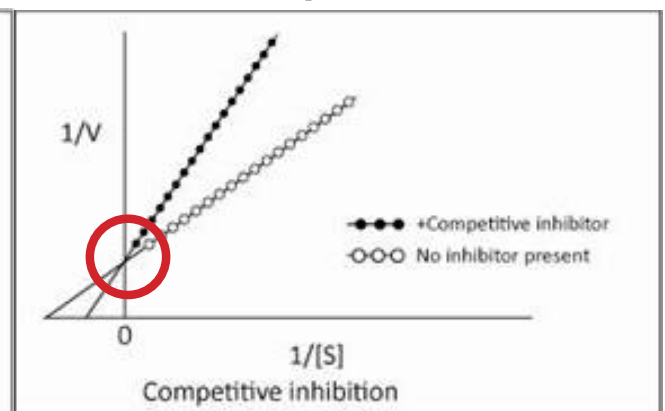
Noncompetitive Inhibition

Competitive Inhibition

**Non-Competitive**

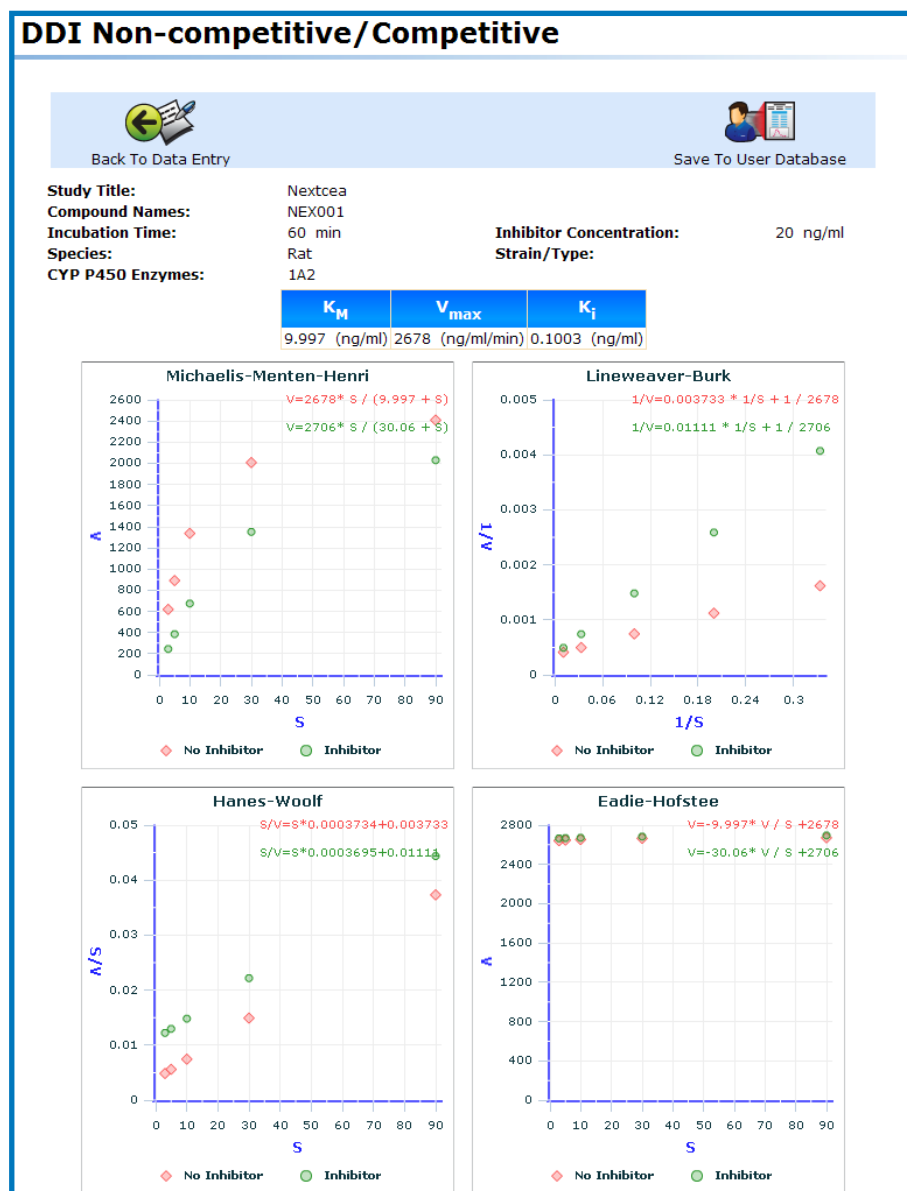


**Competitive**



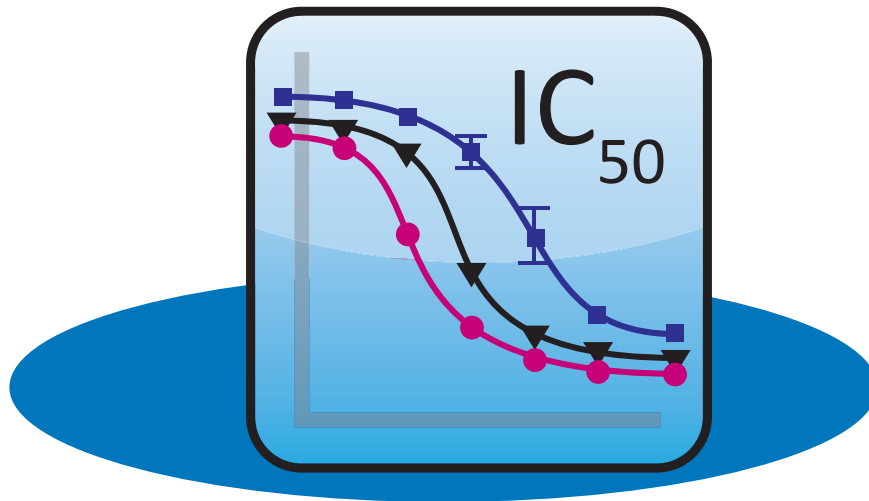
# DDI Non-competitive/Competitive 12 *N*extcea

- 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<sub>50</sub> Determination 13

## 13.1 About IC<sub>50</sub> Determination



This function calculates of the effectiveness of a compound in inhibiting biological function. It calculates the half maximal inhibitory concentration (IC<sub>50</sub>) from submitted substrate concentration information.

### IC<sub>50</sub>

Select user input data format:


Substrate and Inhibitor Conc

	Measured Substrate Conc, [S]	Initial Substrate Conc	Inhibitor Conc
1	<input type="text"/>	<input type="text"/>	<input type="text"/>

# IC<sub>50</sub> Determination 13

## 13.2 Using IC<sub>50</sub> Determination

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

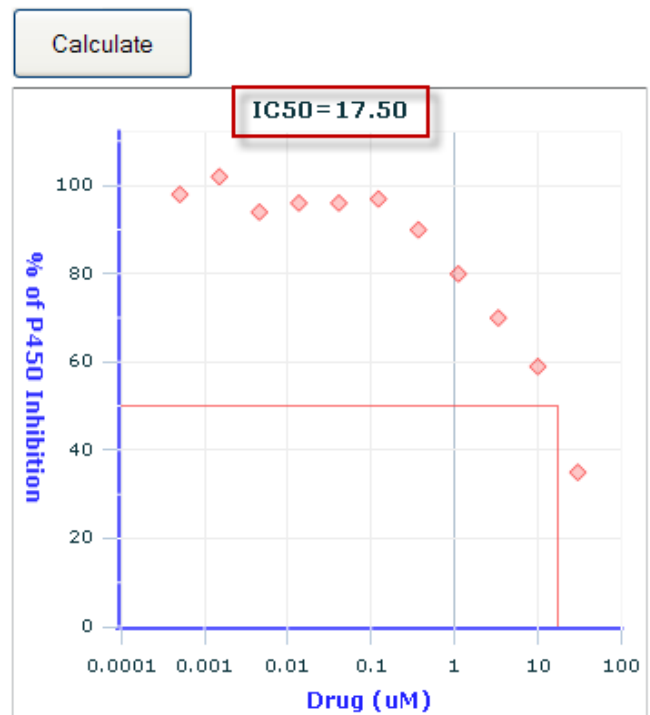
- Click calculation button 
- View results, IC<sub>50</sub> is calculated

### IC<sub>50</sub>

Select user input data format:

% of P450 Inhibition

	% 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		



# Technical Support

For questions or comments about Admetry® Desktop please contact Nextcea:



Admetry@nextcea.com



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(781) 457-4010





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