

# **pkpd notes**

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# **Preface**

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# 1 Introduction to WinNonlin (122-D)

## 1.1 Project setup

### 1. Create Project

Phenoex Projects

- contains all the data and calculations
- multiple projects can be open at the same time
- common data file to import: excel, csv
- older version can always be opened by newer version
- newer version projects can not be opened by older ones
- Create a project
- Click to history tab to see the project history
- Click to properties tab, where most of the work is done

### 2. Create Worksheets

- Right click on Data, select New, select Worksheet
- Add columns, give column name, assign data type
- assign units: select time from list of columns, click Unit Builder button, specify h to the time, click Add button, click OK
- for dose, specify mass prefix, click Add
- Type numbers on the worksheet to add values to the cells

### 3. Import Files

- file type: xls, xlsx, csv, SAS
- typical data file contains header and unit row.
- Select the Import button, select the file
- on the File import wizard, select appropriate options
- Preview area helps to see the changes
- If units are in the column header, select “has units in the header”

Excels with multiple worksheet:

- click the arrow to move on the Wizard to the next worksheet
4. Save Projects
    - Click the save icon on the toolbar
    - File name can be completely different from the Project name
    - No auto-save options
    - sharing project file will also share the embedded data files
    - Close project by right clicking the project name
    - After opening a saved project folder, expand the plus sign to see the contents.
  5. Set Project Preferences
    - Select the Edit menu -> preferences -> Projects
    - Check Autosave on execution
    - update the save locations and hit apply before clicking on OK.

## 1.2 Create and Modify Worksheets

1. Sort Rows
  - data can be sorted by subject, dose level,
  - sort button on every worksheet
  - Use the “sort worksheet” window to apply sort options
2. Move Columns
  - Select a column from the column list
  - Click the up or down arrow to move
3. Rename Columns
  - Click the column name, type F2 or double click on it to edit the name
4. Apply Units
  - Select column
  - Click the Unit Builder
  - Click Clear Units
  - Add units
5. Convert Units

- convert amount column from microgram to miligram
- click the Amount column
- type mg in the New unit box, click OK
- To convert ng/mL to nmole/mL, add nmol and then click the slash button, specify the volume unit, enter molecular weight, click OK.
- Better way: use the Data Wizard to convert the units.

## 1.3 Plot Data

### 1. Create Simple Plot

- Data: Conc, Time, dose level: 16 mg, 10 subjects
- right click the worksheet
- Select send to -> plotting -> xy plot
- XY object is created with the linked data source
- On the mapping window, orange column headers are required mappings
- map, x -> Time, y -> conc, Group -> subject
- click execute
- Options pan - Axes - Y - select log button
- Options pan - Graphs - rename by typing F2
- Graph name and legend names are the same

### 2. Create Lattice Plot

- Data: Conc, Time, Administration, dose level 4 mg for IV, 8 mg for PO, 10 subjects
- Create a XY plot object same as above
- map x - Time, y - conc, group - subject, lattice column - administration
- Execute and get two plots
- Options - range - ‘auto scale best’ settings scales individual plots are independent

### 3. Use Second Y Axis

- Data: plasma conc, urine conc, time, 10 subjects
- Create XY plot object same as above
- map x - Time, y - plasma conc, y2 - urine conc, lattice condition, page (sort) - Subject
- plots are on a single page for each subject
- Options - select plasma\_conc vs Time, type F2, change the name to Plasma, do the same for Urine
- Execute

### 4. Compute Descriptive Statistics

- Needed to create a plot with mean and error bars

- right click on data sheet, send to - computation tools - Descriptive statistics
- map summary - conc, sort - Time
- Execute
- Options pannel - click Clear All - click basic statistics, check Mean and SD

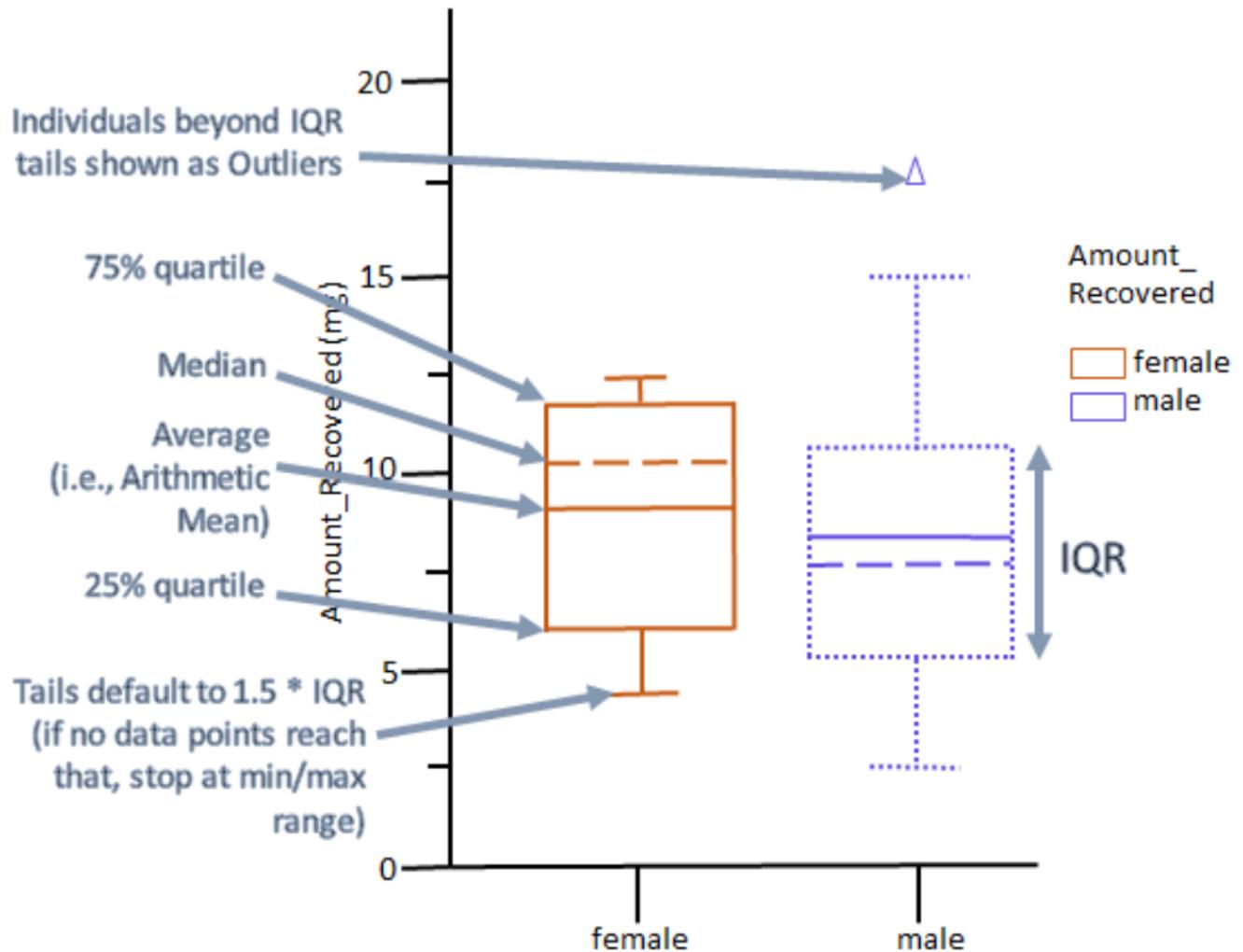
## 5. Use Error Bars

- Descriptive Statistics object - Output data - right click on Statistics
- send to plotting - XY plot
- map x - Time, y - Mean, Error bars, lower - SD, Error bars, upper - SD
- Execute
- set Y axis to log scale

## 6. Create Overlay Plot

- duplicate the error bars plot from previous section
- Options pan - Plot - Graphs tab - click Add button
- Select the new second input from the setup tab
- Link the source data by clicking source button,
- map x - Time, y - conc, group - subject
- Execute
- Options pan - select Conc vs Time plot
- Select Quick Styles
- Uncheck Group by lines, uncheck Gourp by colors,
- Select Apprance tab
- Specify color to Silver
- Uncheck Markers visible
- Now all the individual lines are silver color
- Select Mean vs Time graph
- Select Appearance, specify line colors to red, Marker border color - red, line weight 3
- Under the Mean vs Time graph, select the Error bars
- Select Appearance, color - red
- Options pan - select Y axis - select Axis label and update
- Options pan - select Legend - uncheck Visible

## 7. Create Box Plot



- 20 subjects, AR: accumulation ratio (how much accumulated under repeated ss), dose level, 2 mg and 4 mg
- Is AR increases with increasing dose level?
- right click data, send to - plotting - box plot
- map y - AR, group - dose level
- Execute

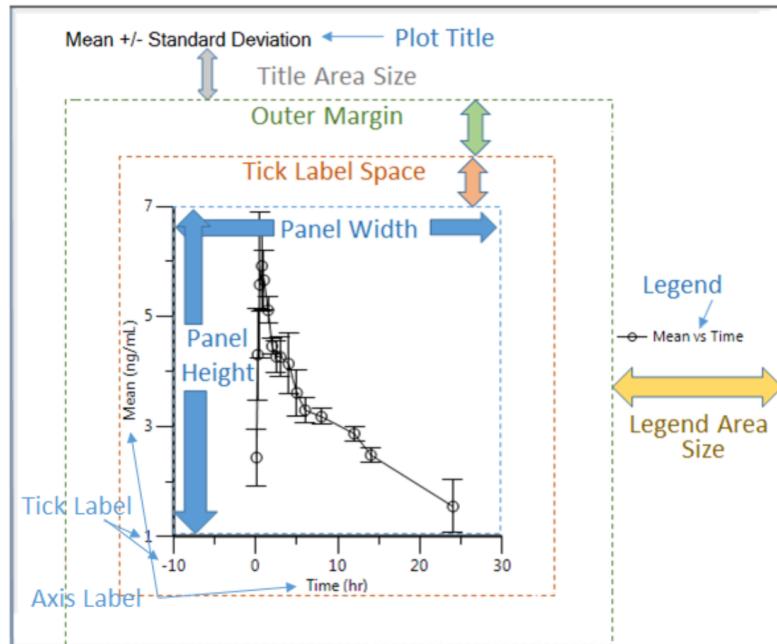
## 8. Create Plot with Categorical X Axis

- Data: Severity (Mild, Moderate), dose level (1, 2, 4, 8, 16, 32 mg), frequency (numerical,

i.e., 0, 0.2, 0.6)

- right click the data sheet, send to plotting - X-categorical XY plot
- map x - severity, y - frequency, group - dose level
- Options pan, select X axis, select Order tab, change order if needed
- Options pan - Frequency vs Severity graph - check line visible - now points are connected by a line

## 9. Set Plot Preferences



- Options pan - Plot - Layout
- Edit menu bar, preferences, plotting details
- Changing preferences affect all new plots

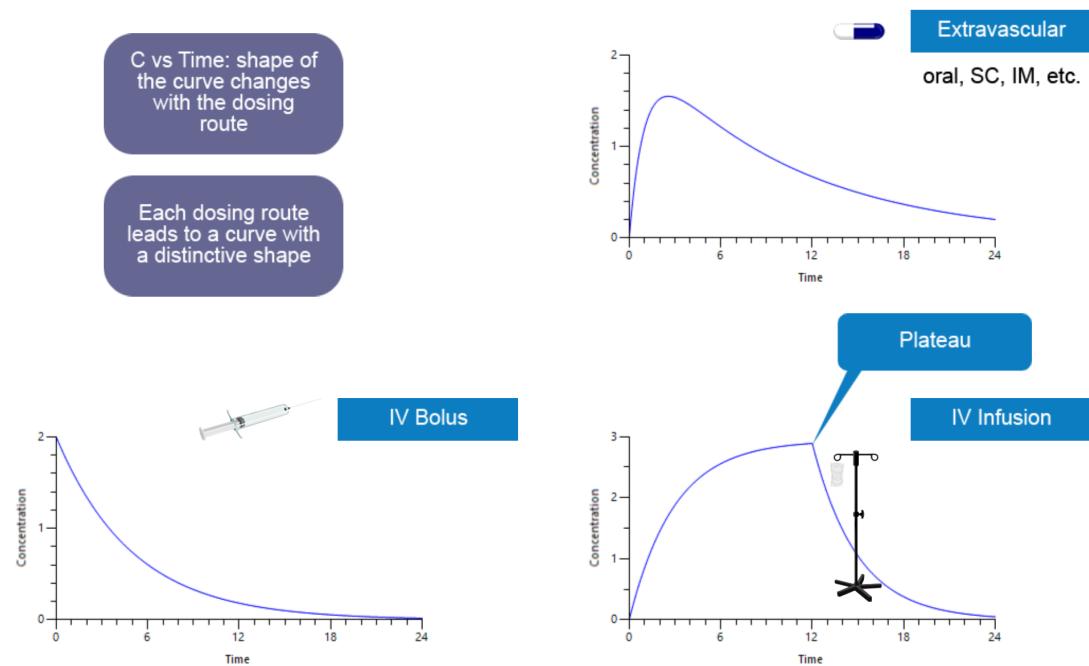
## 1.4 Introduction to NCA

### 1.4.1 About NCA

Non-compartmental analysis or NCA is a method for quantifying drug exposure

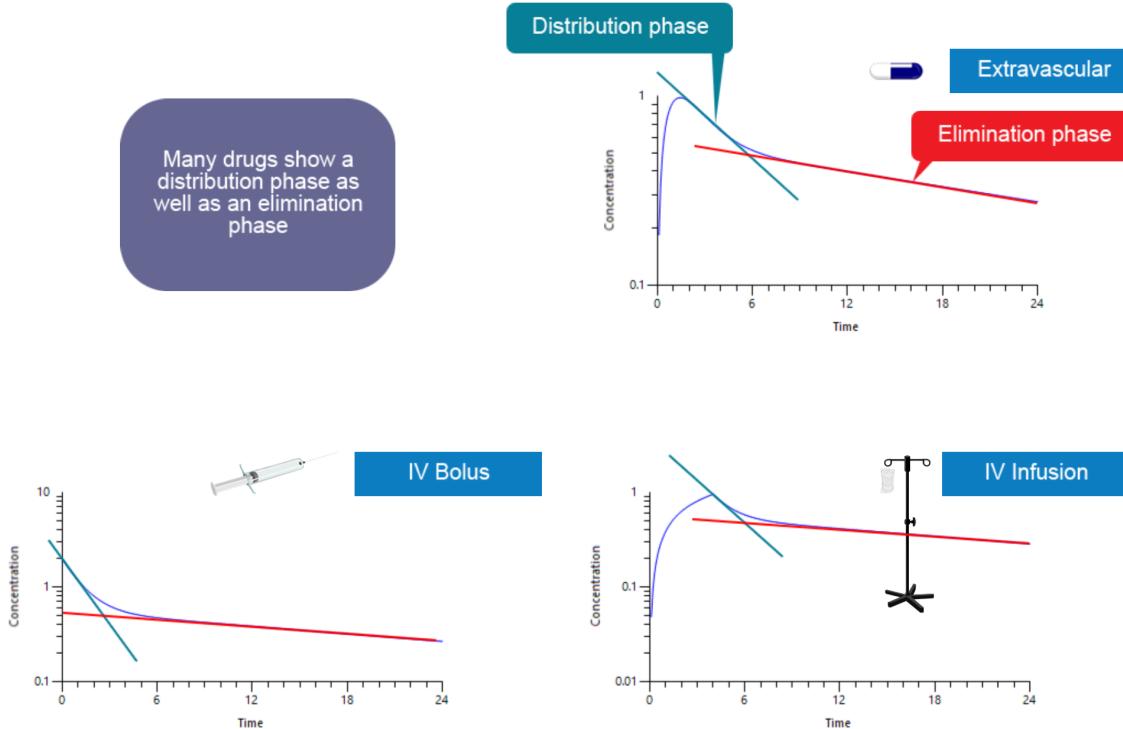
- NCA determines a large number of pharmacokinetic descriptors or PK parameters for a drug
- They are not really parameters as you would have in a model
- NCA does not use any kind of model other than assuming that the elimination can be described by first order kinetics

- because there is no model at the heart of the method we cannot really use it for predictions
- An example plot of concentration over time following an extravascular dose NCA will give us two different measures of drug exposure:
  - the peak exposure to the drug concentration occurring after dosing
  - The overall exposure is measured by computing the area under the curve or AUC
  - an extravascular dose starts with a concentration of zero, the concentration rises rapidly reaches  $C_{max}$  and then decreases



- with extra vascular dosing there is an absorption process that leads to a maximum concentration followed by elimination
- IV bolus dosing: drug is directly injected all at once into a vein; the mixing and systemic circulation is very fast and by the time the first sample is taken after dosing the mixing is assumed to be complete. The concentration starts high and then decreases as the drug is eliminated.
- IV infusion: the concentration starts at zero and then rises if the infusion is continued for long enough the concentration approaches a plateau at steady state when the infusion stops the concentration then falls in the same manner as in ivy bolus dosing

- plotting on a log scale is useful because it usually shows linear elimination in each case regardless of the dosing route we could fit the linear portion with a straight line to predict what will happen to concentration after we've collected the last sample concentration on the log axis



- It is useful to have both linear and log plots. Linear plots are useful for examining the peak concentration and log plots are useful for the low concentrations
- In addition to an elimination phase many drugs also show a distribution phase in such cases there may be two distinctive straight line sections on the plot. Although sometimes the two phases blend into a general curvature in the plots we see here the distribution phase is apparent for all three dosing routes but it is most pronounced for the IV bolus dosing. For extravascular dosing the distribution phase may be obscured by the drug absorption.
- The AUC can be determined no matter how complex the relationship between concentration and time.

Summary:

- NCA is the primary method of assessing drug exposure.
- $C_{max}$  is a measure of peak exposure

- AUC is a measure of the overall exposure to the drug
- different dosing route leads to a curve with the distinctive shape that plotting on a log concentration scale usually shows linear elimination
- many drugs show a distribution phase as well as an elimination phase

#### **1.4.2 Observe Parameters**

- From the plot of concentration versus time, we can see that the maximum concentration is reached at about 1 hour, we call that time  $T_{max}$  and the concentration at the peak is  $C_{max}$
- $T_{max}$  and  $C_{max}$  are listed in the output of NCA in Phoenix
- At some point after dosing we will have our last observed concentration this may be because we have stopped collecting samples or the concentration may have dropped below the quantification limit for the analysis and therefore we were unable to get more values. The point is at a time of  $t_{last}$  and has a concentration of  $C_{last}$ . These observed parameters are affected by the sampling schedule we can improve our chances by sampling richly around the expected time of  $C_{max}$  if we have more points we have a better chance of capturing a concentration that is near the true maximum

Summarize

- Observed parameters are  $T_{Max}$ ,  $C_{max}$ ,  $T_{Last}$  and  $C_{last}$ . We call these observed parameters because they are found directly in the observations
- the observed parameters are dependent on sampling times
- sample richly around the expected time of  $C_{max}$  so you can have a better chance of capturing something close to the true maximum

#### **1.4.3 Half-Life**

- time it takes for the concentration to decrease by 50%.
- a long half-life leads to a shallower slope and a short half-life leads to a steeper slope
- some drugs exhibit two phases a distribution phase and an elimination phase each of these will have a half-life associated with it. The shorter the half-life of the distribution phase the steeper the initial decline will be although we usually concentrate on the half-life of the elimination phase the effective half-life of the drug may very well depend on the half-lives of both of these processes
- It takes five to seven half lives to eliminate the drug.

#### 1.4.4 Area Under the Curve (AUC)

How to calculate AUC?

- assume that the concentration follows a straight line between points
- one triangle and several trapizoid
- AUC is calculated from concentration-time data
- Trapezoids are used to estimate AUC between two data points
- AUC is the sum of the areas of all the trapezoids plus one triangle

#### 1.4.5 Extrapolation to Infinity

- after the  $T_{last}$  there are still large quantity of drug in the plasma
- How can we extrapolate to infinity?
- We need a way to calculate the  $AUC_{T_{last} - \infty}$ .
- Slope of the elimination is the key, apparent terminal phase, magnitide of the slope is  $\lambda_z$

$$AUC_{t_{last}-\infty} = \frac{C_{last}}{\lambda_z}$$

$$AUC_{0-\infty} = AUC_{last} + \frac{C_{last}}{\lambda_z}$$

- extrapolatd area should be below 20%

Important NCA parameters:

- Independent of least-squares fit: such as  $C_{max}$ ,  $T_{max}$ ,  $AUC_{last}$ ,
- Dependent on the least-squares fit:  $\lambda_z$ ,  $AUC_{0-\infty}$ , %Extrapolation, terminal half-life, volume, clearance

#### **1.4.6 Volume of Distribution**

$$C = \frac{Dose}{V}$$

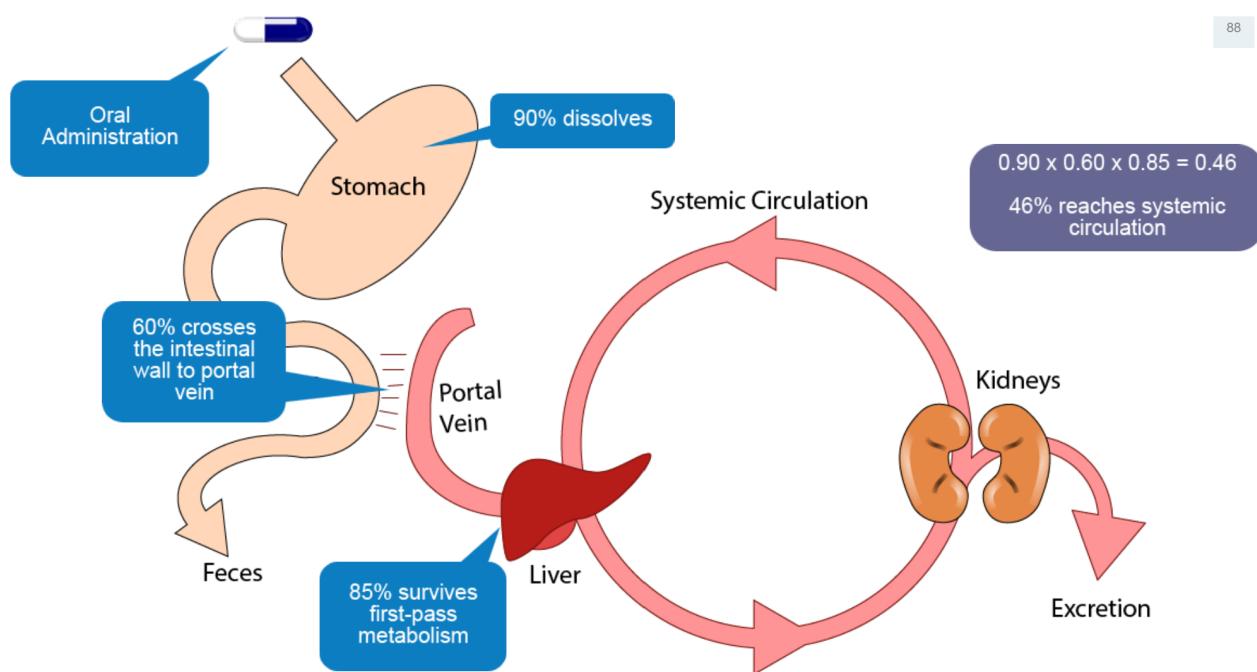
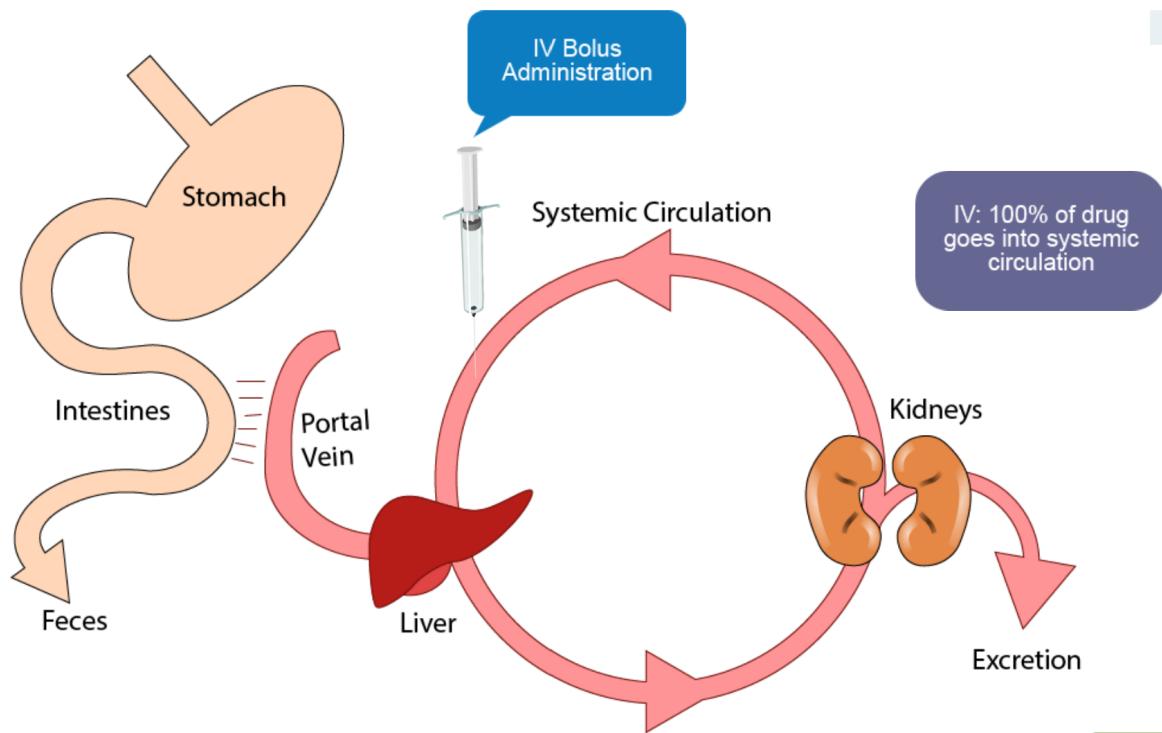
- volume of distribution relates to the dose and concentration
- Does not corresponds to anything physiological
- Example, 100 ug dose to IV bolus and 2 ug/L concentration, volume is 50L.
- typical human plasma volume is 5 L, why V is sometimes very large?
- Drugs that are strongly bound to protein has very high V

#### **1.4.7 Clearance**

- Clearance Quantifies how quickly drug is removed from the body

$$\text{Rate of elimination} = Cl * C(t)$$

- In most cases Cl is constant. If changes with concentration, suspect non linear kinetics (saturation). for this reason, different dose level is administered.
- Clearance includes both Metabolism and Excretion



- it is difficult to obtain all the ratios, so the overall ratio is called Bioavailability.

## Bioavailability

$$F = \frac{AUC_{oral}/Dose_{oral}}{AUC_{IV}/Dose_{IV}}$$

- Intravenous: NCA parameters are V and Cl ( $F = 1$ )
- Extravascular: NCA parameters are  $V/F$  and  $Cl/F$  ( $F < 1$ )
- Elimination = Metabolism (liver) + Excretion (Kidney)
- $Cl_{total} = Cl_{hepatic} + Cl_{renal} + Cl_{other}$
- $Cl_{renal} = A_e$  (amount of drug excreted in the urine) /  $AUC_{plasma}$
- Calculation of Clearance from NCA:

$$\text{Rate of Elimination} = \frac{dA}{dt} = CL \cdot C(t)$$

Total amount of drug reaching circulation  $\int_0^{\infty} dA = CL \cdot \int_0^{\infty} C(t) \cdot dt$  AUC

$$F \cdot Dose = CL \cdot AUC$$

$$\frac{CL}{F} = \frac{Dose}{AUC}$$

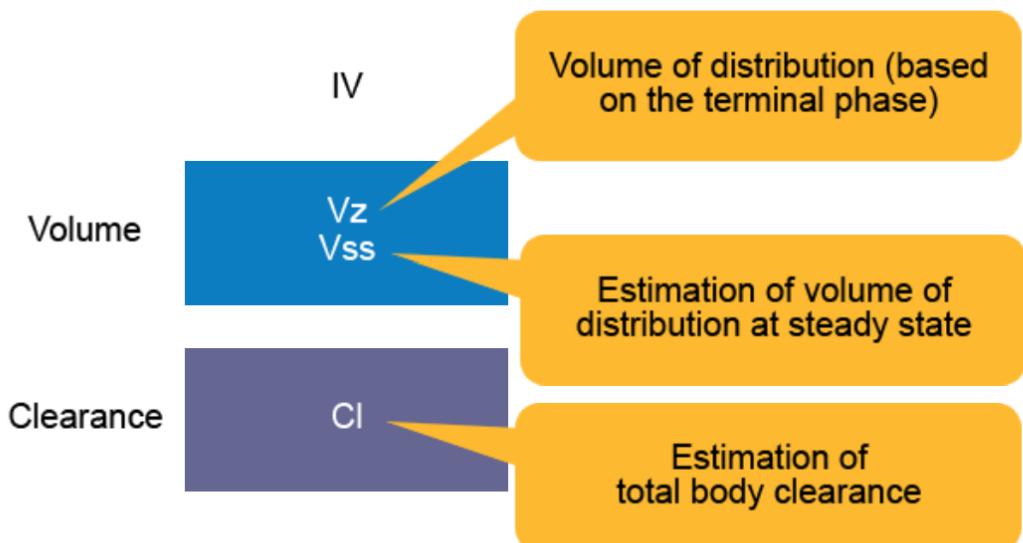
Elimination rate constant

$$k = \frac{CL}{V}$$

Half-life

$$t_{1/2} = \frac{\ln 2}{k} = \frac{\ln 2 \cdot V}{CL}$$

You get the following from NCA



$\frac{(V_z)_{IV}}{F} \approx (V_z/F)_{Ev}$	Volume	IV $V_z/V_{ss}$	Extravascular $V_{z\_F} (V_z/F)$	Volume of distribution, based on terminal phase, not adjusted for bioavailability
$\frac{(Cl)_{IV}}{F} \approx (Cl/F)_{Ev}$	Clearance	Cl	$Cl\_F (Cl/F)$	Total body clearance, not adjusted for bioavailability

#### 1.4.8 Linear vs Log

Method	Trapezoids	Interpolation
Linear Trapezoids Linear Interpolation (default)	Allways Linear	Always Linear
Linear Log Trapezoidal	Linear before $T_{max}$ Log after $T_{max}$	Linear before $T_{max}$ Log after $T_{max}$
Linear Up Log Down	Linear when C rises Log when C falls	Linear when C rises Log when C falls
Linear Trapezoidal Linear/Log Interpolation	Always Linear	Linear before $T_{max}$ Log after $T_{max}$

## 1.5 Run NCA on Plasma Data

### 1.5.1 Run NCA using best fit

- Drug: Gravitix, 10 subjects, a single ascending dose (SAD) study, 6 dose level (1, 2, 4, 8, 16, 32 mg), PO administration

- From the plot each subject grouped by dose level, we see that as the dose increases so do the concentrations in plasma
- we expect that the drug exposure should increase proportionally to the dose
- after we run NCA we will assess *dose proportionality* by examining PK parameters returned by NCA
- Two worksheets: Observations and Dosing. Data on Observatino worksheet: Conc, Time, Subject, Doselevel, Administration, Amount.

Performing NCA:

- Right click on observation worksheet
- select sent to, non-compartmental analysis, NCA
- Select plasma, which is default setting
- specify the dose type the default is extravascular
- Required mappings: Time to time, the conc to concentration, subject to sort, dose level to sort
- select dosing. two options: a worksheet with the dosing information or an internal worksheet
- select source
- click okay
- Map: Time to time, amount to dose, subject and dose level to sort
- specify the calculation method linear up logdown
- click execute
- double click the final parameters pivoted worksheet to open in its own window

Viewing plots:

- select observed y and predicted y versus x
- for subject one dose level 1: 5 points were used in the  $\lambda_Z$  calculation, from 8 hours to the last observation at 36 hours
- The best fit method automatically determines the optimal least squares regression using at least three points
- r-squared is the correlation coefficient of the regression
- r squared adjusted is based on the r squared adjusted for the number of points in the regression

- The number points with the best value of r squared adjusted is used.
- the half-life based on the value of  $\lambda_Z$  is also reported in this case the half life is about 22 hours
- Page 2: this plot is also for subject one but now the dose level is 2 mg
- in this case the best fit method used three points in the calculation
- even though it is the same subject but the half-life based on lambda z is much shorter than for the first dose at only about 15 hours
- Page 3: this plot is for subject one does level 4
- again 3 points were used in the calculation
- the half-life is about 28 hours
- Page 4: this is for subject one those level 8
- this time five points were used in the half-life is 15 hours
- Page 5: now we are up to those level 16 for and half-life is 21 hours
- Page 6: this plot is now at the highest to those level 32 mg
- the half life is lower this time It's 18
- we have seen it's quite a variability between different dose levels but is there a systematic trend?

let's create a box plot to see if there is appears to be a trend

- right click on final parameters pivoted
- send to plotting: box plot
- map HL\_lambda\_z to y
- now we want to look for a trend across the dose group map to dose level
- click execute button
- The plot shows us the distribution of half-life across the different dose groups
- from the plots we can see that although there is a good deal of variation in the dose levels, there does not appear to be a systemic trend and all the boxes overlapped with each other

Box plot of AUCs

- let's make the duplicate of this plot:
- right click box plot

- select copy
- right click on the workflow
- select paste
- select the duplicated plot let's change the mapping for the y map AUCINF\_D\_obs
- click execute
- because the data are dose normalized AUC values extrapolated to infinity we would expect these values to be the same for all dose groups and they do appear to be very consistent
- most values falling between 0.04 and 0.05
- this does suggest that the overall drug exposure is proportional to the dose
- although this is not a statistical test for the dose proportionality, it does give us a quick visual impression

Box plot of AUClast\_D

- Let's make duplicate of the second plot right click the plot select copy right click on workflow paste
- map AUClast\_D to y execute

### 1.5.2 Customize rules and parameters

- Goal is to add  $\lambda_Z$  acceptance rules to our NCA
- select the rules tab
- enter 0.9 for r-squared adjusted
- enter 20 for percentage of extrapolation
- enter 2 for span, the span is the number of half lives spent by the regression.
- click execute
- Review the flag column for r-squared adjusted, % extrapolation and span
- note that the results are not removed from the output
- but we can use data tools to do the filtering if we want to

To filter the data:

- Right click in the final parameters pivoted worksheet

- Select sent to
- select data management
- select split worksheet
- map the three flag columns to sort
- Click execute

The “unique values” worksheet shows how many rows there are for each combination of sort values - notice that there are 24 rows that passed all criteria

- let's look at the worksheet fully accepted here we see the walls that has all three criteria is

#### *User defined parameters*

- select “user defined parameters” tab
- to compute the concentration at a time of 48 hours
- enter 48 in the box The other thing that we can do is user defined parameters
- the NCA does include many parameters we can also define our own
- click add button
- add a parameter, i.e., AUC\_2
- For definition you see last / 2
- if you would like this values include in the final parameters pivoted worksheet turn on include the final parameters
- execute the NCA object

#### **1.5.3 Customize slope selections**

- start with NCA used in previous section
- Duplicate the NCA object
- select slopes selector from the Setup tab
- Each plot is on a separate page, on each plot we can see the points that were used select for best fit.
- click the left point to change starting point for the linear fit
- to change the end of the fitting, holding down the shift key and clicking on the indicated point

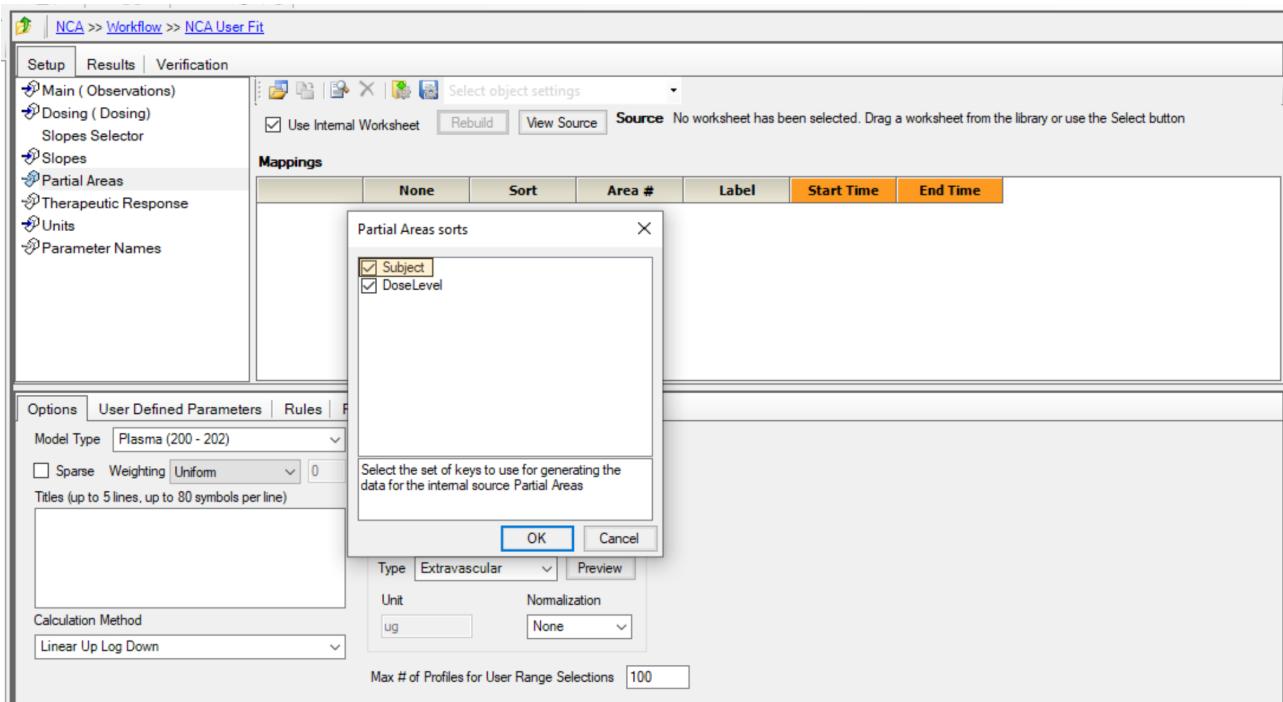
- Don't change the endpoint of the fitting unless you have reason to reset the last point
- to exclude points from the linear fit hold on the control key and click on the indicated point

Faster way of modifying slopes:

- select the slopes under the Setup tab
- this worksheet has the same information we saw in the individual plots but all on one table
- to control the best fit method select rules tab
- we have two options for customizing you can either limit the number of points used in the linear regression or you can specify your start time limit
- Since there is a distribution phase we might decide to make sure that we do not include from the 12 hours in linear regression
- type of 12 in the option start not before
- let's look at the slopes and then see output settings
- select slope settings
- Now, the start time is at least 12 hours
- Comparing box plots from two NCA results ( best fit and coustom fit) it is seen that some of the outliers are removed.
- It is good idea to examine each slopes and adjust the solpes to compare the data.

#### **1.5.4 Compute partial areas**

In the previous section we saw how comparing AUClast was problematic. When different subjects had different Tlast, Computing partial areas is a way that can overcome that limitation.



- Select the setup tab
- Select Partial Areas
- Check “use Internal Wroksheet”
- Beacause we will use the same partial areas for all subjects, uncheck subject checkbox and beacause we want to use the same settings for all dose groups, uncheck DoseLevel checkbox
- Click OK
- We may want to compute more than one partial area, at the bottom of the option tab, we can specify how many we want.
- Click on the selector for number of maximum partial areas. Select 2
- Once again, we are asked to specify the sorts, Uncheck subject and dose level checkbox.
- We need to fill in the start and end times
- For the first partial area, we will compute the partial area for the first 12 hours
- Specify 0 for the start time and 12 for the end time.
- For our second partial area, use 0 and 24 hours.

- If desired, we can label for each partial area. However, label is not required and it will automatically generate for us. Leave the label field blank.
- Click Execute.

The partial areas are added as columns to the right of the final parameters pivoted.

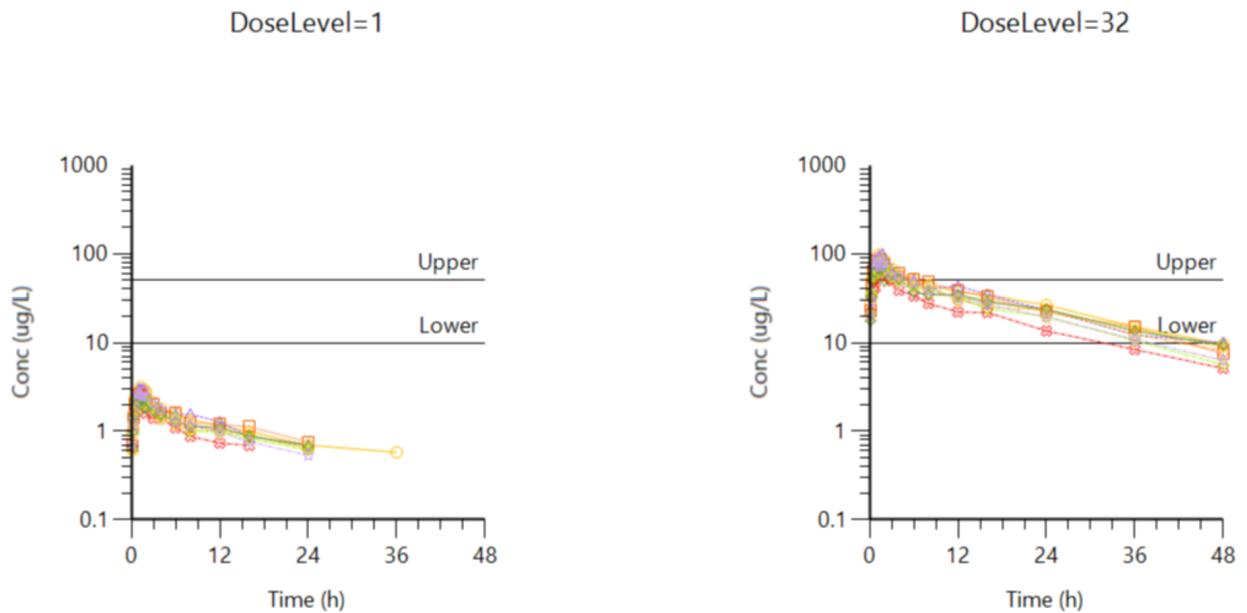
Let's repeat the process for other NCA object in our project: Select NCA best fit Click Setup Click Partial Areas Check "Use Internal Worksheet"

Turn off Subject and doselevel Specify the maximum number of partial areas

The plots are all read, because the plots are all out of date -WE can update by Selecting the workflow in the object browser, the Workflow is displayed, click the Execute button and it will update. While the Workflow is selected, on the result tab, we have the output of the workflow. Let's go back to the workflow diagram, select Diagram, notice how the red color gone

### 1.5.5 Use Therapeutic response

To choose a dose for a given drug we have consider both the efficacy and side effects. We can set upper and lower concentration limits in NCA and quantify the time and AUC between the limits as well as above and below.



The following plot is for gravitex SAD study: Let's say we want concentration to be between 10 and 50 ug/L. At the lowest dose, all the concentrations are below the lower limit. For higher dose (32 mg), concentrations are largely between the upper and lower limit

- Select “Therapeutic Response” option on the Setup tab of the NCA object
- uncheck both subject and dose boxes
- Enter 10 for lower limit and 50 for higher limit
- Execute

### **1.5.6 Customize units and parameters names**

To obtain units in the NCA results, we need to have units defined on the concentrations, the times and the doses

- concentration units are microgram per liter, nanogram per liter and micromols per liter
- times units are typically either hours or minutes and in some cases days
- units for doses are milligrams micrograms and micromols
- it is not recommended to mix mass units
- if you get no units on your results you may have missed the unit on the concentration, time or dose, you will see the message insufficient unit in the units output. If this happens to you check that you have proper units on the concentration time and dose

Define the units used in the NCA:

- select the setup tab
- select the units input
- The default units depend on input dataset units because the time units in the input data set is hours all the time units in the NCA results will also be based on hours
- The volume unit in our input data is liters and therefore all the results have liters in the default units
- if we decide we want to change the units on our results we can do so by changing the values in the columns labeled preferred

let's do that

The screenshot shows the Phoenix NCA software interface. The main window title is "NCA >> Workflow >> NCA User Fit". The left sidebar has tabs for "Setup", "Results", and "Verification". Under "Setup", there are sections for "Main (Observations)", "Dosing (Dosing)", "Slopes Selector", "Slopes", "Partial Areas", "Therapeutic Response", "Units", and "Parameter Names". The "Parameter Names" section is currently selected. In the center, there is a table titled "mL" with columns "Name", "Default", and "Preferred". The rows are numbered 1 to 13. Row 9 (Volume) has "mL" in the "Preferred" column. A yellow callout bubble with the text "mL" points to this cell. A green button labeled "Submit" is located to the right of the table. At the bottom of the interface, there are tabs for "Options", "User Defined Parameters", "Rules", "Plots", "Properties", "Information", and "History".

	Name	Default	Preferred
1	Dosing_time, Tau, Lz_times	h	h
2	Tmin, Tmax, Tlast, Tlag	h	h
3	Cmin, Cmax, Clast, Clast_pred, Ctau, Cavg, C(t)	ug/L	ug/L
4	Cmax / D	ug/L/ug	ug/L/ug
5	Lambda_z	1/h	1/h
6	Terminal halflife	h	h
7	AUC (last, all, inf, resp. windows)	h*ug/L	h*ug/L
8	AUC / D	h*ug/L/ug	h*ug/L/ug
9	Volume (Vz, Vz/F, Vss)	L	mL
10	Clearance (CL, CL/F, CLss/F)	L/h	L/h
11	AUMC (last, inf)	h*h*ug/L	h*h*ug/L
12	MRT (last, inf)	h	h
13	Response windowtimes	h	h

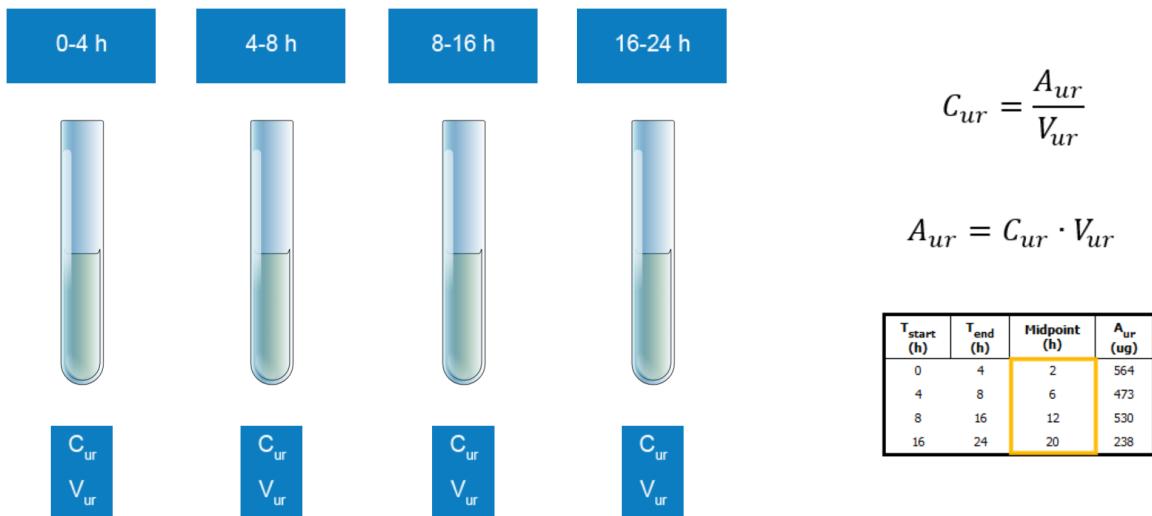
- Change the preferred unit for volume to milliliter
- specify milliliters per minute for the clearance unit
- Make sure to match the case as shown
- Phoenix will attempt to convert but if Phoenix doesn't know how to convert to your preferred unit it will revert to the default unit execute the NCA
- By checking execute here you can see the appropriate units in the results.

#### Changing Parameters Name

- Click setup tab select the parameter names input
- Turn on the Use internal worksheet checkbox
- Let's say that we want to change the name of half life
- And executed the NCA and now the half-life column has been renamed in the result

## 1.6 Run Urine NCA

### 1.6.1 About Urine NCA



$$C_{ur} = \frac{A_{ur}}{V_{ur}}$$

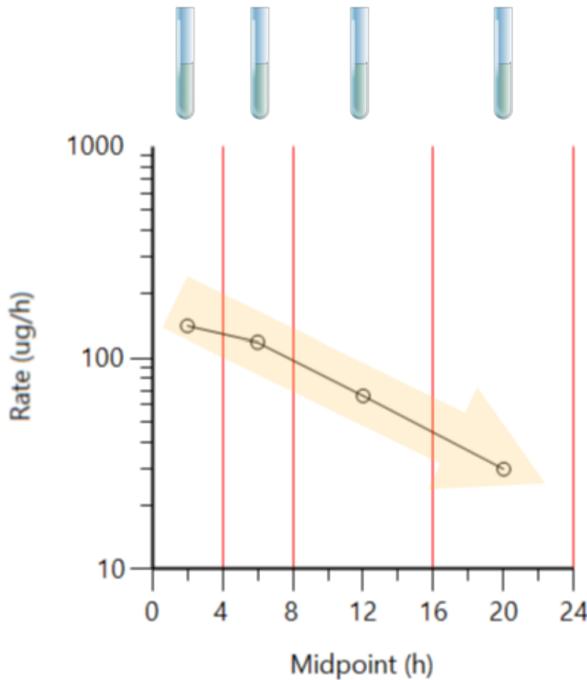
$$A_{ur} = C_{ur} \cdot V_{ur}$$

T <sub>start</sub> (h)	T <sub>end</sub> (h)	Midpoint (h)	A <sub>ur</sub> (ug)
0	4	2	564
4	8	6	473
8	16	12	530
16	24	20	238

- Urine samples are collected over an interval. Four samples were collected and concentration was measured, the data is compiled in the table.
- The rate of drug excretion is calculated by:

$$Rate = \frac{A_{ur}}{t_{end} - t_{start}}$$

- Plot the Rate of drug excretion vs midpoint of collection interval
- Rate of excretion starts high and decreases over time.



- Most import parameters are Amount Recovered and Percent Recovered and Percent of extrapolation (AURC\_%Extrap\_red)
- Urine NCA also include lambdaZ and halflife, however, since the urine data only contains four data, it is better to use plasma halflife
- Percent of extrapolation should be as small as possible.

### 1.6.2 Setup project

- 10 subjects, dose level, 4 mg, conc in both plasma and urine,

### 1.6.3 Exploratory Data Analysis

- XY plot of plasma conc vs time is created
- XY plot of urine conc vs time is created. Time is end of collection interval

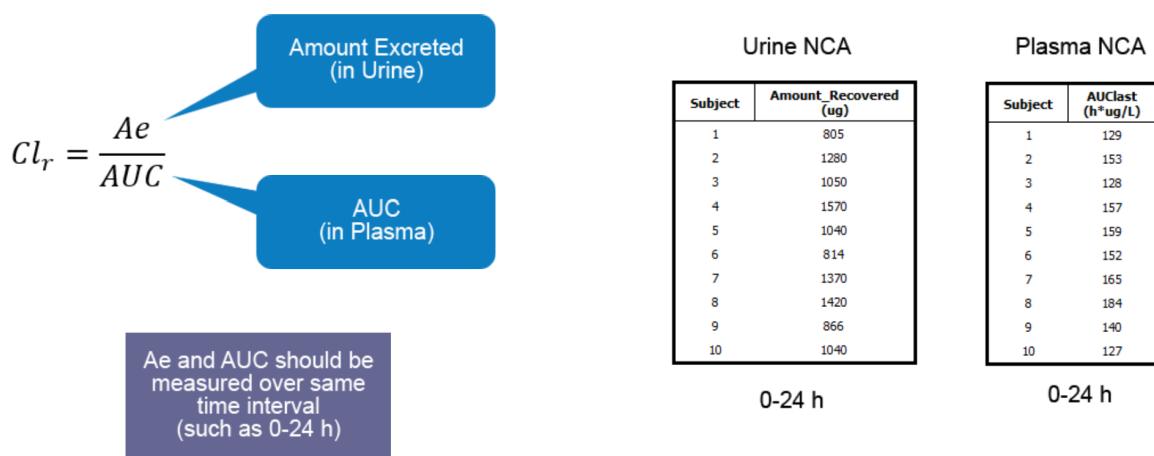
#### 1.6.4 NCA of plasma data

- map x to Time, y to conc, sort to subject
- select the Dosing input, map Time to Time, Dose to dose, sort to subject
- Select linear up log down
- Execute

#### 1.6.5 NCA of urine data

- specify the model type: Urine
- Required mapping: start time, end time, concentration, volume
- sort to subject
- select the dosing file, sort subject
- Execute
- Automatic data calculations was done. Three different rates are given: Max\_rate, Rate\_last, Rate\_last\_pred, Tmax\_rate, AURC: Area Under the Rate Curve
- Urine NCA does not extrapolate for amount recovered and percent recovered. That's why it is best to collect urine samples until no more drugs are detected in the urine sample

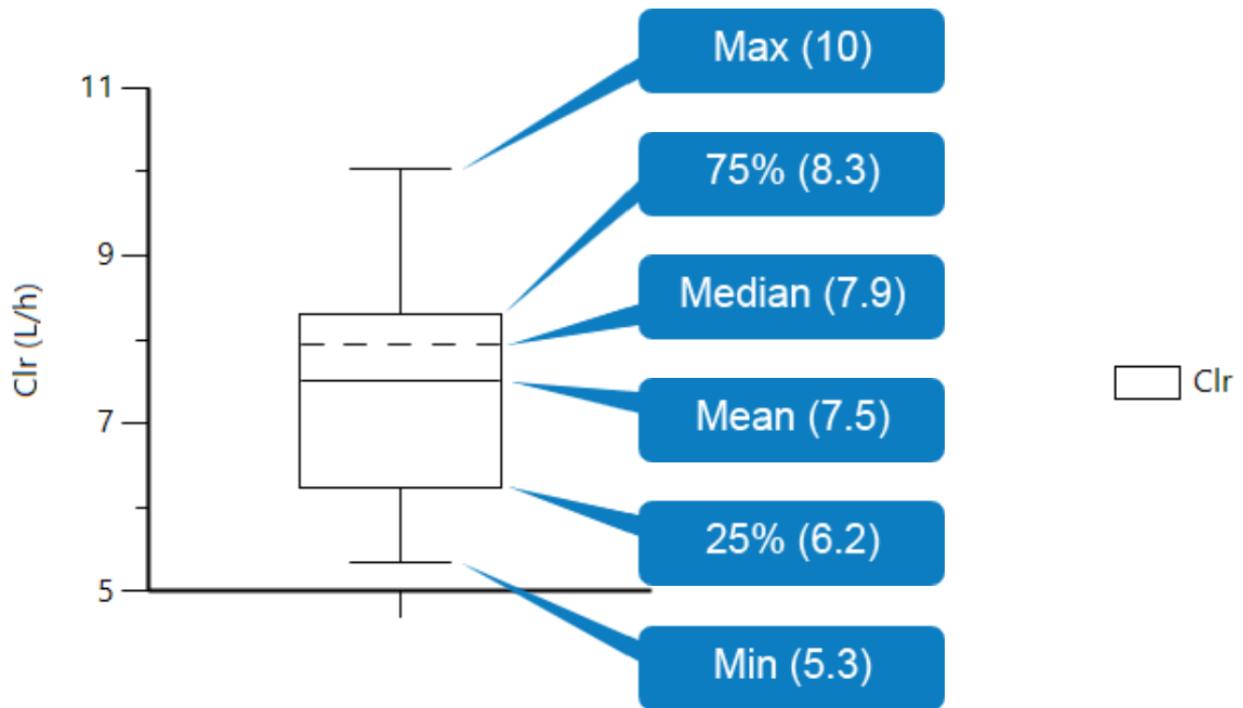
#### 1.6.6 Calculate Renal Clearance



- right click Final Parameter Pivited, send to “computation tools”, “ratio and differences”.
- map sort to subject
- Select the worksheet2 input, click to select source button, select “Final Parameter Pivited” from NCA plasma, sort to subject
- On the options tab, update the X column to “Amount Recovered”, Y column: AUClast, new column name: Clr, unit: L/h,
- Execute

Create a box plot

- Right click Ratios Differences Stacked, send to box plot, map y to Clr,



## 1.7 Sparse and Steady-State NCA

- pre-clinical study of Gravtex in rats, 20 rats, dose: 200 ug/kg, time of blood draws: group A(0.5, 1, 2, 4, 8 h), group B( 0.75, 2, 6, 12 h)
- Not possible to do full NCA with only four data points

- We need to pool the data to do NCA
- Data: Schedule ( group A or group B), Animal, Time, Conc

### **1.7.1 EDA of Sparse Data**

Plot: Concentration vs time by schedule

- Plotting the data: XY plot, map x to Time, y to conc, group to schedule, group to animal
- Options pan, select the graph Conc vs Time, select Quick Style tab, check “Each group to color”, select “Schedule”
- Now the lines are yellow for group A and purple for group B.
- Turn off “group by marker”, now all the markers are same
- Turn off “group by lines”,
- Select the Legend and turn off the “visible” checkbox

Table:

- right click observation worksheet, send to reporting, select table
- map conc to Data, animal to Raw ID, Raw Stratification to Schedule, Column Stratification to Time.
- Select “Precision/Alignment” from option, precision method: significantDigits, value: 3,
- For Time, specify the precision method: DecimalPlaces, value: 2, execute
- Select Animal column, specify precision method: DecimalPlaces, value: 0
- Select statistic tab, turn of “mean” and “SD”

### **1.7.2 NCA of Sparse Data**

Key Points on NCA of spares data:

- Spares Option often used in pre-clinical data, where there is insufficient data to compute a full NCA for each subject
- Once set of PK parameters is returned for the pooled results
- PK parameters are identical to what you would get by running NCA on mean concentration data

- Standard errors on  $C_{\max}$  and  $AUC_{\text{last}}$ . These are calculated using published methods
- Standard error calculation is only available with linear trapezoids

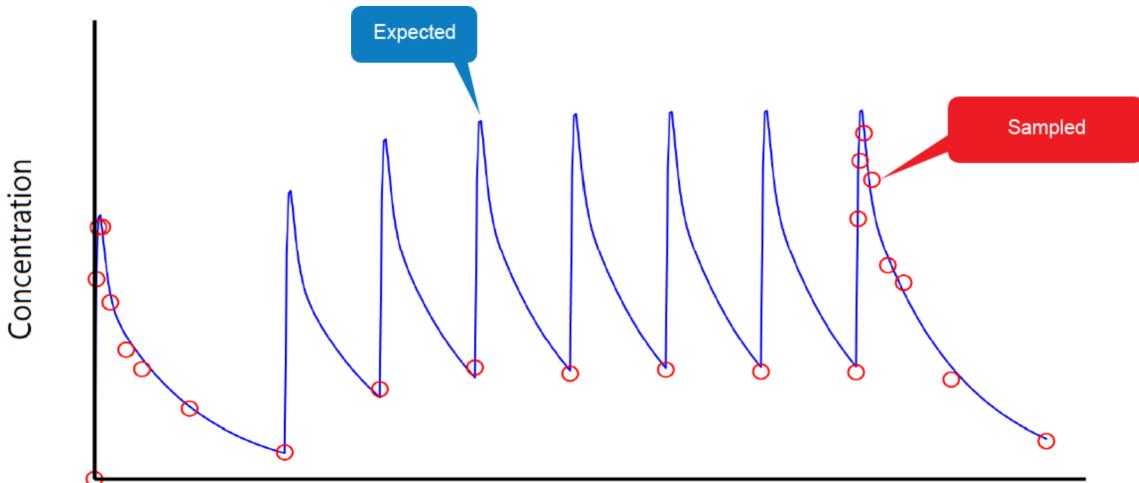
Perform NCA

- Send the data to NCA, turn on “Sparse” button
- Required mapping: Time to time, Concentration to Conc and Subject to Animal
- Specify dosing file, time to Time and dose to dose\_norm, execute
- There is only one raw in the result sheet
- Linear Trapizoid method was used and SE was obtained for some of the PK parameters.
- Since the data is pooled, only one plot is obtained.

### 1.7.3 EDA of Multiple-Dose Data

Study design:

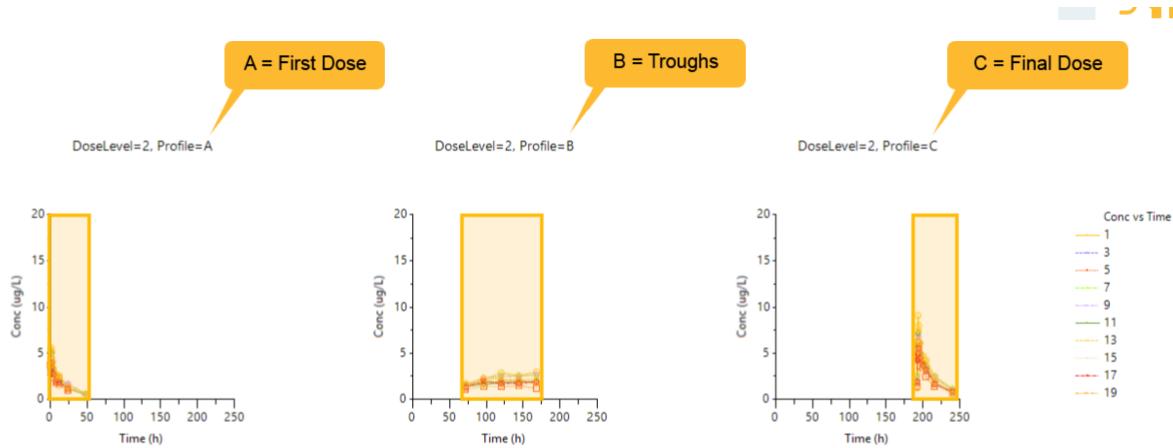
- Example: Gravitex multiple dose study
- 20 human subjects randomly divided into two groups (dose level 2 and 4), dosed at 0h, conc. determined at 48 h, 2nd dose at 48h, next doses at every 24h, until 192 hours. The first dose is a Naive dose
- Richly sampled for 0 to 48 hours and the last dose from 192h to 240h. Only Trough conc were measured for other doses



Blue lines are generated from PK model.

Plots:

- Map x to Time, y to Conc, group to subject, lattice page to dose level, lattice column to profile



After modifying (log) x and y axis:

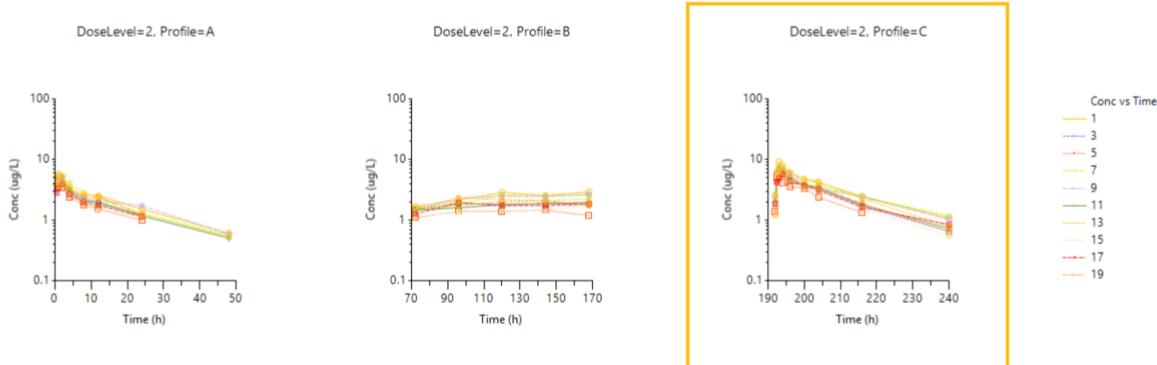


Table:

- Send to reporting, Table
- map Data to Conc, subject to RowID, dose level to stratification row, stratification column to time, profile to stratification column.
- Select Column/sort Order, select Row Stratification, select Column Stratification, move profile to the top,

		Profile																							
		A								B								C							
		Time (h)		Time (h)		Time (h)																			
DoseLevel (mg)	Subject	0.0	0.5	1.0	2.0	4.0	8.0	12.0	24.0	48.0	72.0	96.0	120.0	144.0	168.0	192.0	192.5	193.0	194.0	196.0	200.0	204.0	216.0	240.0	
Conc (ug/L)																									
2	1	BQL	5.13	5.61	5.26	3.25	2.67	2.56	1.53	0.61	1.71	2.15	2.89	2.58	2.97	2.63	6.14	9.10	8.02	6.11	4.73	4.20	2.51	1.09	
	3	BQL	3.48	4.40	4.41	3.07	2.24	1.90	1.22	BQL	1.55	1.93	1.83	1.90	1.86	1.85	4.55	5.56	6.05	5.23	3.72	3.42	1.73	0.66	
	5	BQL	3.70	4.39	3.53	2.38	1.80	1.56	0.99	BQL	1.10	1.42	1.41	1.47	1.21	1.41	5.06	5.21	4.23	3.58	3.39	2.39	1.35	BQL	
	7	BQL	3.73	4.53	3.80	3.54	2.27	1.86	1.28	0.57	1.57	1.86	2.62	2.52	2.61	2.54	6.09	7.45	7.41	4.67	3.92	3.72	2.43	1.19	
	9	BQL	3.30	4.11	3.97	2.94	2.28	2.12	1.75	0.60	1.46	2.38	2.49	2.47	2.72	2.37	5.27	6.89	6.74	5.93	4.04	3.40	2.43	1.03	
	11	BQL	4.39	5.03	5.23	2.05	2.02	1.19	0.51	1.48	1.61	1.82	1.90	1.98	2.01	5.80	7.17	5.97	4.42	3.91	3.34	1.82	0.73		
	13	BQL	3.55	5.46	4.77	4.05	2.80	2.47	1.28	0.54	1.61	2.35	2.21	2.13	2.24	2.24	5.75	7.50	7.47	5.80	4.58	4.34	2.29	0.79	
	15	BQL	3.66	4.64	4.21	2.57	1.96	1.45	1.18	BQL	1.13	1.39	1.44	1.48	1.74	1.78	5.27	6.44	5.28	4.23	3.35	3.12	1.56	0.55	
	17	BQL	2.85	3.46	4.00	2.69	1.97	1.78	1.15	BQL	1.28	1.96	1.76	1.75	1.86	1.89	4.28	4.92	5.56	4.36	3.75	3.15	1.65	0.85	
	19	BQL	3.74	4.55	4.01	3.22	2.37	2.38	1.24	BQL	1.52	1.78	2.04	2.08	1.82	1.25	5.79	6.32	6.22	4.87	3.84	3.57	1.88	0.66	
4	2	BQL	8.18	11.32	12.15	7.87	5.83	5.24	2.95	1.16	3.39	4.85	4.17	4.77	4.69	4.32	12.54	16.70	11.70	11.06	10.10	8.01	4.27	1.63	
	4	BQL	7.67	10.23	8.44	7.26	5.19	4.79	2.89	1.00	3.39	3.89	4.42	4.60	4.40	5.04	11.94	13.70	14.12	11.30	8.32	7.53	4.65	1.75	
	6	BQL	8.03	8.26	8.86	5.80	4.60	4.05	2.31	0.84	2.62	3.37	3.80	3.62	3.52	3.76	10.50	12.03	9.87	9.47	7.46	5.80	3.78	1.54	
	8	BQL	8.00	9.17	8.10	5.73	4.79	3.97	2.38	0.72	2.43	3.42	3.29	4.03	2.97	3.49	10.96	13.71	11.63	9.49	8.59	6.30	3.33	1.07	
	10	BQL	7.99	10.48	10.86	7.36	5.50	4.39	2.54	0.76	2.56	3.05	3.40	3.48	2.94	3.52	10.04	12.14	12.34	11.92	7.62	7.19	2.95	1.11	
	12	BQL	7.37	10.10	7.85	5.71	4.28	4.50	2.85	1.48	3.80	4.12	4.68	4.68	5.20	5.54	13.35	14.72	12.17	9.03	9.20	7.07	5.35	2.02	
	14	BQL	7.42	8.31	9.65	6.19	4.94	3.22	2.16	0.93	2.65	3.89	3.52	3.91	3.58	3.90	10.24	12.26	13.50	8.98	8.29	6.92	3.97	1.51	
	16	BQL	8.03	10.30	9.05	6.68	4.79	4.47	2.13	0.83	2.99	3.22	3.74	4.00	3.35	4.14	11.38	11.90	11.22	9.88	7.58	6.60	3.38	1.26	
	18	BQL	6.14	8.42	7.99	5.09	4.36	3.59	2.27	0.76	2.29	3.00	3.22	2.93	3.27	9.51	8.99	9.89	8.80	6.12	5.88	3.21	1.13		
	20	BQL	7.26	7.83	9.07	6.02	4.98	4.16	3.10	1.12	3.09	3.67	3.74	4.82	4.02	4.26	10.91	12.20	11.62	9.80	8.72	6.83	4.61	1.82	

### 1.7.4 Split Data

- Before running NCA of multiple dose data, we need to split data
- Right click the worksheet, send to Data Management, Split Worksheet
- map profile to sort, Execute.
- Split the dose worksheet the same way as the observation worksheet

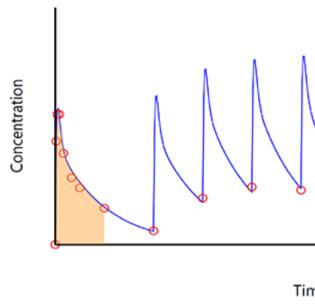
### 1.7.5 NCA for First Dose

- Select Split Observation, right click on Output data A, send to NCA
- map subject to sort, dose level to sort, conc to concentration, time to Time
- link dosing input for A profile
- map Dose to Amount, Tau to Tau, sort to dose level and subject
- Calculation method LinearupLogdown
- Select Dose level column and click freeze pane icon

### 1.7.6 NCA for Final Dose

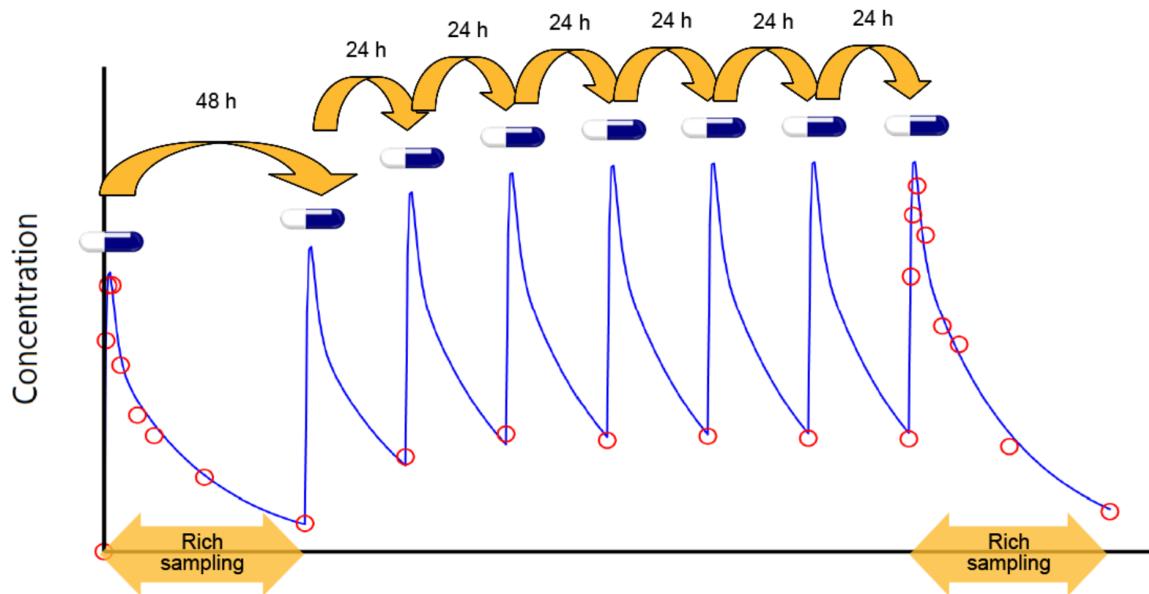
- perform same operation as for First Dose by selecting profile C.
- $T_{min}$  is the time where minimum concentration was found
- $C_{tau}$  is the concentration at the end of the dosing interval
- $C_{avg}$  is the average concentration during the dosing interval

DoseLevel (mg)	Subject	Tlast (h)	AUClast (h*ug/L)	AUC_TAU (h*ug/L)
2	1	240	148	107
	3	240	109	82.9
	5	216	63.9	63.9
	7	240	135	93.6
	9	240	133	93.6
	11	240	112	83.2
	13	240	137	103
	15	240	98.3	75.0
	17	240	106	76.7
	19	240	114	85.9
<b>Mean</b>		<b>238</b>	<b>116</b>	<b>86.5</b>
<b>SD</b>		<b>7.59</b>	<b>24.3</b>	<b>13.2</b>
4	2	240	264	198
	4	240	263	192
	6	240	216	156
	8	240	213	165
	10	240	216	171
	12	240	271	189
	14	240	234	173
	16	240	215	163
	18	240	190	142
	20	240	251	179
<b>Mean</b>		<b>240</b>	<b>233</b>	<b>173</b>
<b>SD</b>		<b>0.00</b>	<b>27.5</b>	<b>17.2</b>



- Difference between  $AUC_{last}$  and  $AUC_{tau}$
- Slope correction of the linear fit is of concern only if we are extrapolating the results. Otherwise  $AUC_{tau}$  will not be affected by the slope correction.

### 1.7.7 Determine Accumulation Ratio



NCA can only determine PK parameters of the first dose or the last dose,  
Accumulation ratio (AR) is calculated with the equation below:

$$AR = \frac{AUC_{\tau,SS}}{AUC_{0-\tau}}$$

where,  $AUC_{\tau,SS}$  is AUC\_TAU from steady-state NCA, last dose and  $AUC_{0-\tau}$  is AUC0\_24 partial area from first dose NCA  
partial area

## 1.8 Use Data Tools

### 1.8.1 Append Worksheets

- Combine data from two worksheets that share the same general structure of columns

**PK1**

	Subject	AUC
<b>1</b>	1	1000
<b>2</b>	2	2000
<b>3</b>	3	3000



**PK2**

	Subject	AUC
<b>1</b>	1	200
<b>2</b>	2	500
<b>3</b>	3	700

**Result**

	Source	Subject	AUC
<b>1</b>	PK1	1	1000
<b>2</b>	PK1	2	2000
<b>3</b>	PK1	3	3000
<b>4</b>	PK2	1	200
<b>5</b>	PK2	2	500
<b>6</b>	PK2	3	700

- example, combine PK1 and PK2. The new column “source” tells which worksheet each set of rows came from.
- Columns do not have to be identical nor the same order
- Right click the worksheet, select Data Management, Append Worksheets
- map source column to all the columns of worksheet 1
- Click worksheet2, link the source file, map all the columns to Source Column
- Double click Results tab to view the results
- To append more than one worksheet, set the number on the option section

### 1.8.2 Cross-product Worksheets

- For making combination of multiple columns,

Worksheet1

	Subject
1	1
2	2
3	3

Result

	Subject	Time (h)
1	1	0
2	1	4
3	1	8
4	1	24
5	2	0
6	2	4
7	2	8
8	2	24
9	3	0
10	3	4
11	3	8
12	3	24

Worksheet2

	Time (h)
1	0
2	4
3	8
4	24



- Right click the worksheet, send to Crossproduct Worksheet
- map subject to sort
- Link the second worksheet and map the same way as before, Execute

### 1.8.3 Join Worksheets

- To combine data so that rows are matched by a common sort key. Merge option is identical to Join option.

Worksheet1

	Subject	AUC
1	1	1000
2	2	2000
3	3	3000

Result

	Subject	AUC	Treatment
1	1	1000	A
2	2	2000	B
3	3	3000	C

Worksheet2

	Subject	Treatment
1	1	A
2	2	B
3	3	C



Merge is very similar

[X]

Worksheet 1 (Observations)

Worksheet 2

Sort Map

Select object settings

Source Use Data Tools.Data.BP.Observations

View Source

Mappings

	None	Sort	Source Column
Subject	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Time	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
BP	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

Source Data

	Subject	Time (min)	BP ({mm_Hg})
1	1	0	190
2	1	10	190
3	1	25	189
4	1	60	186
r	1	75	182

Mapping Output Sort Order

The screenshot shows the Data Tools interface with the following components:

- Mappings:** A table where columns are mapped from source data to target columns.

	None	Sort	Source Column
Subj	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Treatment	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
- Source Data:** A table showing the raw data used for mapping.

	Subj	Treatment
1		A
2		B
3		A
4		B
5		B

- both column has be to same name to join the columns.
- Click 'sort map", turn on Internal Worksheet, cut and paste to the same row.

Setup Results Verification

Filter: \_\_\_\_\_

**Output Data**

**Result**

**Text Output**

**Settings**

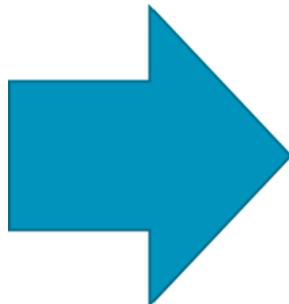
	Subject	Subj	Time (min)	BP ({mm_Hg})	Treatment
1	1	1	0	190	A
2	1	1	10	190	A
3	1	1	25	189	A
4	1	1	60	186	A
5	1	1	75	182	A
6	1	1	90	179	A
7	1	1	120	175	A
8	1	1	180	172	A
9	1	1	210	167	A
10	1	1	300	162	A
11	2	2	0	198	B
12	2	2	10	198	B
13	2	2	25	197	B
14	2	2	60	193	B
15	2	2	75	185	B
16	2	2	90	179	B
17	2	2	120	167	B
18	2	2	180	157	B
19	2	2	210	145	B
20	2	2	300	135	B

#### 1.8.4 Pivot Worksheet

- Rearranging data to allow comparison, for example to compare the effect of treatment, we need to see the data:

Source Worksheet

	Subject	Trt	AUC
1	1	A	100
2	1	B	1000
3	2	A	150
4	2	B	1500
5	3	A	300
6	3	B	3000



Pivoted Worksheet

	Subject	A	B
1	1	100	1000
2	2	150	1500
3	3	300	3000

Mappings							
	None	Column Header	Values	Row Header	Unit	Carry	Attribute
Route	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dose_Type	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Time	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Conc	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Source Data							
	Route	Dose_Type	Time (min)	Conc (ug/L)			
1	IV	IV Bolus	10	4.7			
2	IV	IV Bolus	15	4.48			
3	IV	IV Bolus	20	4.22			
4	IV	IV Bolus	30	3.87			
5			40				
6			60				
7			90				
8			120				
9			180				
10			210				
11			240				
12			300				
13			360				

	Time (min)	IV (ug/L)	PO (ug/L)
1	10	4.7	0
2	15	4.48	0.28
3	20	4.22	0.55
4	30	3.87	1.2
5	40	3.57	2
6	60	2.97	1.95
7	90	2.25	1.85
8	120	1.74	1.6
9	180	1.02	0.86
10	210	0.77	0.78
11	240	0.61	0.6
12	300	0.36	0.21
13	360	0.2	0.18

### 1.8.5 Stack Columns

- Inverse of Pivoting . Stackers stacks two or more column into a single column

SOURCE Use Data Tools.Data.IV and Oral.Wide

**Mappings**

	None	Carry	Stack
Time	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
Oral	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
IV	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>

**Source Data**

	Time (min)	Oral (ug/L)	IV (ug/L)
1	10	0	4.7
2	15	0.28	4.48
3	20	0.55	4.22
4	30	1.2	3.87
5	40	2	3.57

- Change the column names from the options section
- 

### 1.8.6 Split Worksheet

### 1.8.7 Enumerate Worksheet

- To convert text values to numbers,

Source Worksheet

	ID	Gender
1	1	male
2	2	female
3	3	male
4	4	female
5	5	male
6	6	female

Enumerated

	ID	Gender	Gender_code
1	1	male	0
2	2	female	1
3	3	male	0
4	4	female	1
5	5	male	0
6	6	female	1

Use Data Tools >> Workflow >> Enumerate Worksheets

Setup    Results    Verification

Worksheet (Trt Groups)    Output Column Names    User Supplied Values

Select object settings

Use Internal Worksheet    Rebuild    View Source

	Enumerate Column	Value	Output Value
1	Treatment	A	1
2	Treatment	B	2
*			

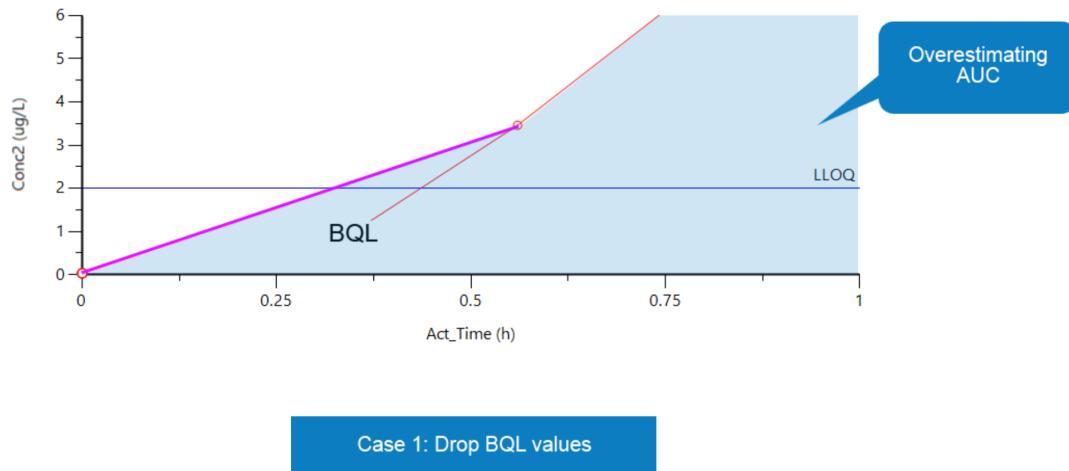
### 1.8.8 Make BQL Substitutions

	Subject	Act_Time (h)	Nom_time (h)	Conc (ug/L)
1	1	0.28	0.25	7.78
2	1	0.57	0.5	16.59
3	1	1.2	1	36.05
4	1	2.07	2	54.22
5	1	4.1	4	66.32
6	1	6.16	6	46.89
7	1	8.06	8	39.11
8	1	12.17	12	21.61
9	1	24.35	24	NS
10	1	48.67	48	3.01
11	1	98.06	96	BQL
12	1	144.93	144	BQL
13	2	0.3	0.25	BQL
14	2	0.56	0.5	4.4
15	2	1.01	1	12.66
16	2	2.33	2	32.72
17	2	4.23	4	67.78
18	2	6.04	6	60.64

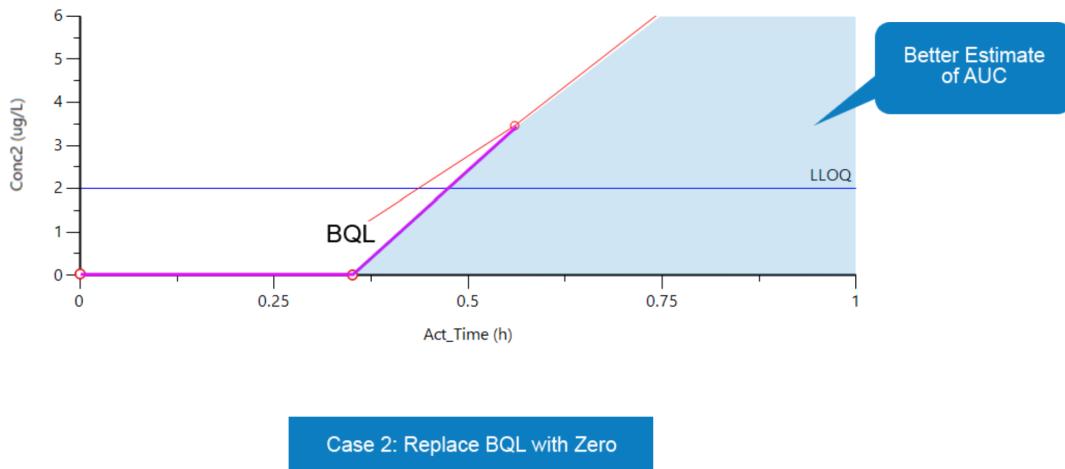
	Subject			
	1	2	3	4
Nom_time (h)	Conc (ug/L)			
	0.250	7.78	BQL	BQL
0.500	16.6	4.40	3.46	3.41
1.00	36.1	12.7	11.7	24.1
2.00	54.2	32.7	29.8	30.0
4.00	66.3	67.8	45.0	60.3
6.00	46.9	60.6	NS	58.2
8.00	39.1	51.3	31.0	56.5
12.0	21.6	32.0	19.5	24.2
24.0	NS	8.43	3.67	BQL
48.0	3.01	3.57	2.20	2.58
96.0	BQL	BQL	BQL	BQL
144	BQL	BQL	BQL	BQL

BQL = Below Quantification Limit  
NS = No Sample

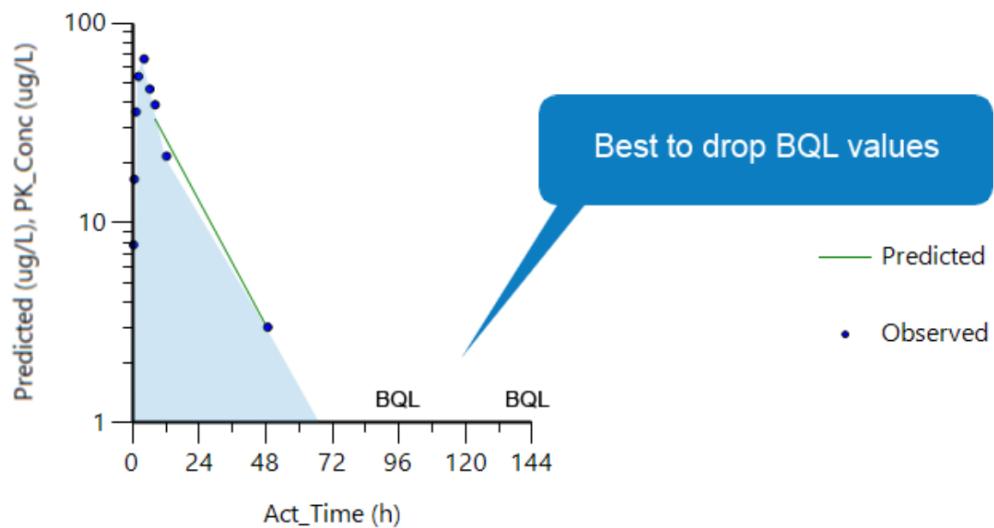
- Any non-numeric data is ignored by the NCA object



- To estimate  $T_{lag}$  we must replace BQL by zero



Subject=1  
 $R^2=0.983$   $R^2_{adjusted}=0.966$   $HL_{Lambda\_z}=11.6411$   
 3 points used in calculation



		Conditional Substitution								
		Nonnumeric Code	Unconditional Substitution	Before Tmax	After Tmax	First Consecutive After Tmax	After First Consecutive After Tmax	All Entries After 2 Consecutive - After Tmax [Optional]	Use When < LLOQ	Set to LLOQ and censor
1	BQL			0	Missing	Missing	Missing		<input type="checkbox"/>	<input type="checkbox"/>
2	NS	Missing							<input type="checkbox"/>	<input type="checkbox"/>
*									<input type="checkbox"/>	<input type="checkbox"/>

NCA does not distinguish non-numeric codes  
(it ignores all non-numeric values)

Setup | Results | Verification

Main (BQL Data) Rule Set

Select object settings

View Source Source: BQL Data.BQL Data

Mappings

	None	Sort	Time	Concentration	Status Code	LLOQ	Carry
Subject	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Act_Time	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Nom_time	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
Conc	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Mapping Output Sort Order

Output Column Name: PK\_Conc

Carry Over Concentration Column

Nom_time (h)	Subject			
	1	2	3	4
0.250	7.78	BQL	BQL	BQL
0.500	16.6	4.40	3.46	3.41
1.00	36.1	12.7	11.7	24.1
2.00	54.2	32.7	29.8	30.0
4.00	66.3	67.8	45.0	60.3
6.00	46.9	60.6	NS	58.2
8.00	39.1	51.3	31.0	56.5
12.0	21.6	32.0	19.5	24.2
24.0	NS	8.43	3.67	BQL
48.0	3.01	3.57	2.20	2.58
96.0	BQL	BQL	BQL	BQL
144	BQL	BQL	BQL	BQL

BQL = Below Quantification Limit  
NS = No Sample

Nom_time (h)	Subject			
	1	2	3	4
0.250	7.78	0.00	0.00	0.00
0.500	16.6	4.40	3.46	3.41
1.00	36.1	12.7	11.7	24.1
2.00	54.2	32.7	29.8	30.0
4.00	66.3	67.8	45.0	60.3
6.00	46.9	60.6	Missing	58.2
8.00	39.1	51.3	31.0	56.5
12.0	21.6	32.0	19.5	24.2
24.0	Missing	8.43	3.67	Missing
48.0	3.01	3.57	2.20	2.58
96.0	Missing	Missing	Missing	Missing
144	Missing	Missing	Missing	Missing

Source Data

BQL Output

## 1.9 Compute Ratios and Differences

### 1.9.1 Compute Ratios from Single Input

- 10 subjects with 2 mg IV dose, after wash out period same subject was administered 4 mg PO, To compute Bio-availability, we need to do ratio from a single worksheet.

The screenshot shows the WinNonlin software interface with two main windows. The top window is titled 'Worksheet 1 (NCA.Final Para...)' and displays the 'Mappings' and 'Options' tabs. The 'Mappings' tab shows a grid of parameters: Administration, Subject, N\_Samples, Dose, Rsq, and Rsn\_adjusted. The 'Options' tab shows a table for defining the X/Y comparison, with columns for Comparison, Column, Filter Value, and Description. The 'Comparison' row is set to 'X/Y' with 'AUCINF\_D\_pred' in the X column and 'IV' in the Y column. The 'Description' column contains the formula: AUCINF\_D\_pred where Administration = PO / AUCINF\_D\_pred where Administration = IV. The bottom window is titled 'Verification' and shows a table of 'Output Data' under the 'Ratios Differences' section. The table has columns for 'Subject' and 'F'. The data rows are numbered 1 to 10, corresponding to the 10 subjects, with values ranging from 0.54150724 to 0.71011965.

Subject	F
1	0.66862383
2	0.69894928
3	0.66959047
4	0.65611522
5	0.54150724
6	0.60701935
7	0.62142119
8	0.71011965
9	0.61750686
10	0.70820232

### 1.9.2 Compute Ratios from Dual Inputs

- NCA for urine and plasma must be done in separate NCA object, we have to combine results from two different worksheets.
- Renal Clearance example, view clearance section above.

The screenshot shows the WinNonlin software interface with the 'Results' tab selected. In the top left, there are tabs for 'Setup', 'Results', and 'Verification'. Below the tabs, there are icons for opening files, saving, and exiting, along with a 'Select object settings' dropdown. The 'Source' dropdown indicates 'Mapped to result of: Ratios from Two Sources Workflow.Plasma NCA.Final Parameters Pivoted'. The 'View Source' button is also visible.

**Mappings**

	None	Sort	Filter	Carry
Subject	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>
N_Samples	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Dose	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rsq	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rsq_adjusted	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Corr_XY	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
No_points_lambda_z	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**Options**

The 'Add' button is highlighted. Below it is a table:

Comparison	X		Y		New Column Name	Units	Description
	Worksheet	Column	Worksheet	Column			
X/Y	Worksheet 1 (Final Parameters Pivoted)	Amount_Recovered	Worksheet 2 (Final Parameters Pivoted)	AUC0_72	Clr	ug/(h*ug/L)	Final Parameters Pivoted.Amount_Recovered / Final Parameters Pivoted.AUC0_72

### 1.9.3 Compute Ratios using Means

- Difference between cross-over and parallel study

Crossover Study

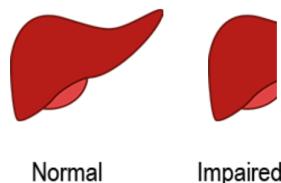
Parallel Study

Bioequivalence



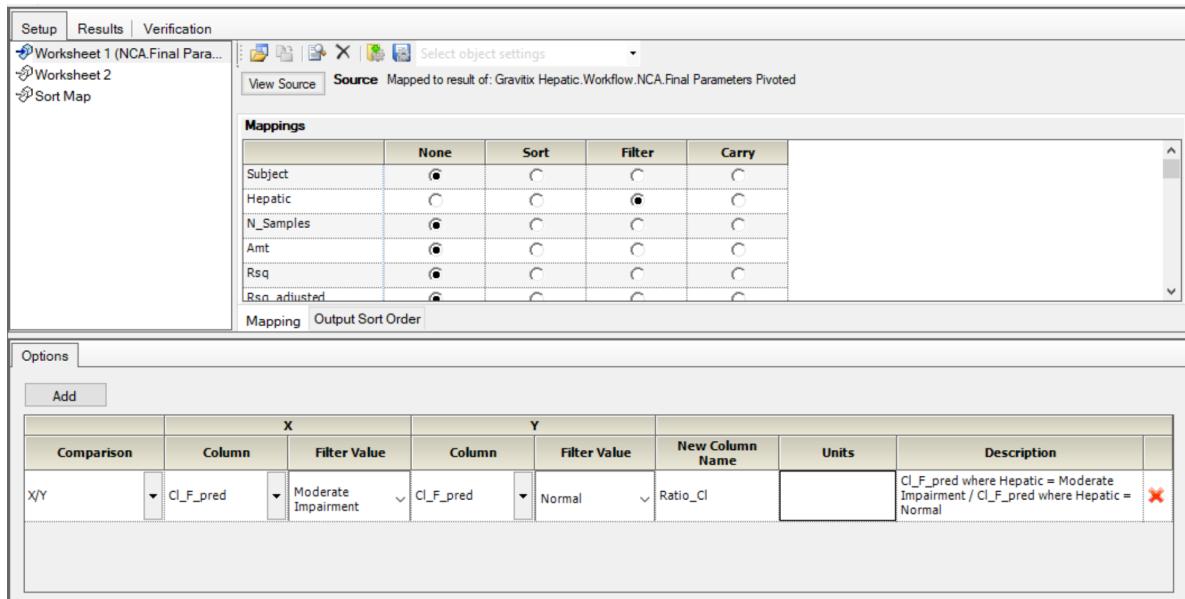
Can calculate individual ratios

Hepatic Impairment



Can only compute ratio of mean values

Also Bioavailability & Renal Clearance



The screenshot shows a software interface for NCA analysis. The top menu bar includes 'Setup', 'Results', and 'Verification'. Under 'Setup', there are three worksheets: 'Worksheet 1 (NCA.Final Para...)', 'Worksheet 2', and 'Sort Map'. The 'Source' button is highlighted, indicating it is mapped to 'GravitiX Hepatic.Workflow.NCA.Final Parameters Pivoted'. The main area contains two sections: 'Mappings' and 'Options'.

**Mappings:**

	None	Sort	Filter	Carry
Subject	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hepatic	<input type="radio"/>	<input checked="" type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
N_Samples	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Amt	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rsq	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rsd_Adjusted	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

**Options:**

X	Y	New Column Name	Units	Description		
X/Y	Cl_F_pred	Moderate Impairment	Cl_F_pred	Normal	Ratio_Cl	Cl_F_pred where Hepatic = Moderate Impairment / Cl_F_pred where Hepatic = Normal

GravitiX Hepatic >> Workflow >> Ratios and Differences

**Setup**   **Results**   **Verification**

Filter:

**Text Output**

- Settings
- Warnings and Errors

1 Multiple values were found for a profile for X and/or Y values, and the ratios or differences cannot be computed. Revise the Sort and X/Y Filter mappings to further subset the data, or select the option to use means.

2

3

**Options**

Add

X		Y			
Comparison	Column	Filter Value	Column	Filter Value	New Column Name
X/Y	Cl_F_pred	Moderate Impairment	Cl_F_pred	Normal	Ratio_CI

Use means for X and Y when non-unique

#### 1.9.4 Compute Differences

Setup   Results   Verification

Worksheet 1 (NCA.Final Para...   Select object settings

Worksheet 2

Sort Map

**Mappings**

	None	Sort	Filter	Carry
Subject	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Hepatic	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
N_Samples	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Amt	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rsq	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Rsq_adjusted	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Mapping   Output Sort Order

**Options**

Add

X		Y			
Comparison	Column	Filter Value	Column	Filter Value	New Column Name
X/Y	Cl_F_pred	Moderate Impairment	Cl_F_pred	Normal	Ratio_CI
X-Y	Cl_F_pred	Moderate Impairment	Cl_F_pred	Normal	Diff_CI

Use means for X and Y when non-unique

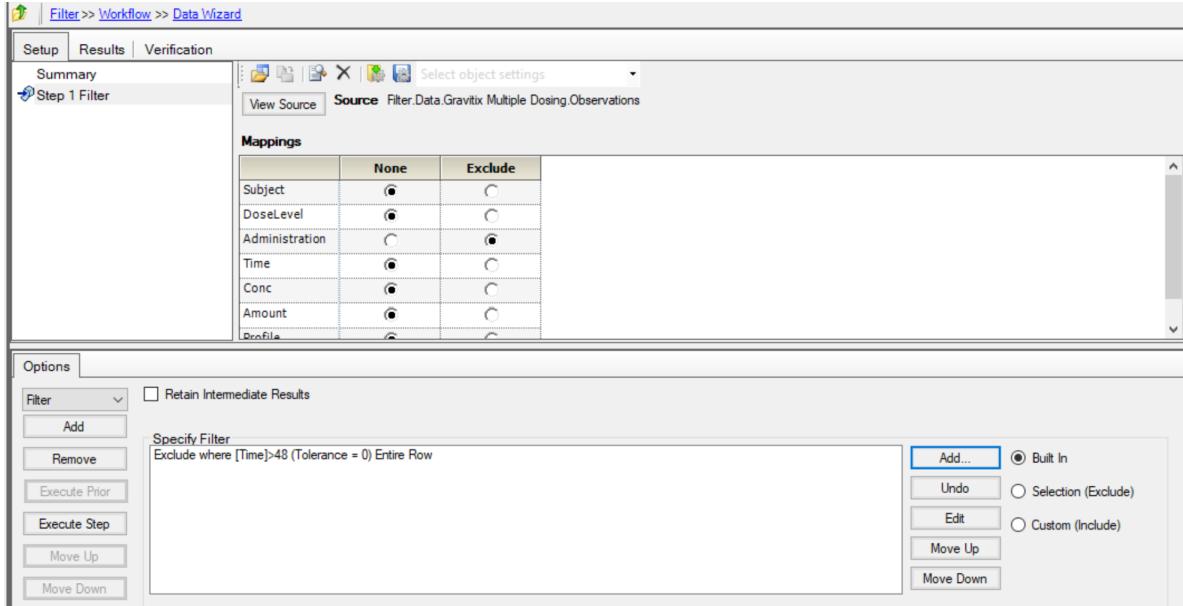
Properties   Information   History

## 1.10 Use Data Wizard

### 1.10.1 Create a Filter

- Filter by time values
- Right click, send to Data management, Data Wizard

### Set Column Properties



- We can: 1. Exclude whole column; 2. Exclude or include by values, 3. Filter individual cells or whole rows.

### 1.10.2 Set column properties

- This can be used to sort columns, rename columns, specify or convert units

### 1.10.3 Transform Data (Arithmetic)

- used to do simple arithmetic; x and y are variables, n is constant, units inherited from source.
- same as data normalization.
- Set baseline in Time based data, Requires Time and Data Columns to map, Substrat the initial values

#### 1.10.4 Transform Data (Custom)

- Ceiling, random

Formula	Mappings	Description
$(A + B) / 2$	A and B	Adds A and B, and then divides by 2
$\ln(\text{Conc})$	Conc	Determines the log of the concentration
<code>if(A=0, "BQL", A)</code>	A	Replaces zero values with "BQL" in column mapped to A

#### 1.10.5 Transform Data (Functions)

- this works with only one single column such as X to  $\ln(X)$ .

#### 1.10.6 Multi-step operation

### 1.11 Applications of NCA

#### 1.11.1 Using Cmax and AUC to Make Decisions

In regulatory guidance:

Rate of absorption :  $C_{\max}$

Extent of absorption: AUC

$C_{\max}$  and AUC are used in the following type of studies:

Table 1.1: Application of NCA

Studies	what compares
Formulations	Compare two formulations of a drug
Food effects	Compare effect of food on drug absorption
Drug-drug interaction	Compare effect of one drug on another
Demographics	Compare effect of demographics (age, weight, gender, etc) on a drug
Special Patient Populations	Compare effect of drug in two different groups
Hepatic Impairment	Compare effect of drug in two different groups
Bio availability	Compare drug exposure with and without absorption
Dose Propportionality	Test of linear kinetics

AUC Ratios (Also for  $C_{max}$  )

$$\text{Bioequivalence } \frac{AUC_{test\ form}}{AUC_{ref\ form}}$$

$$\text{Food Effect } \frac{AUC_{fed}}{AUC_{fasted}}$$

$$\text{Drug-drug Interaction: } \frac{AUC_{Drug+Inhibitor}}{AUC_{Drug\ alone}}$$

$$\text{Hepatic Impairment: } \frac{AUC_{with\ impairment}}{AUC_{normal\ hepatic\ function}}$$

### 1.11.2

#### 1.11.3 Study Designs

Study design considerations:

1. Population
2. Duration
3. Schedule
4. Procedures

Crossover: Each subject receives each treatment

Parallel: Each subject receives one treatment

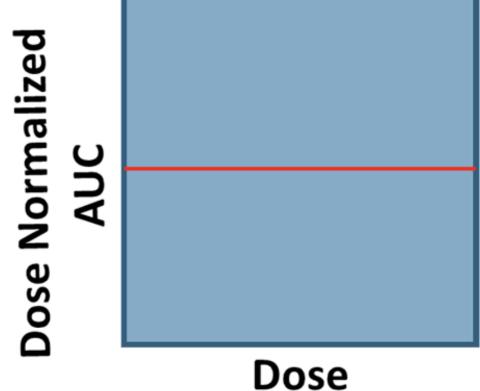
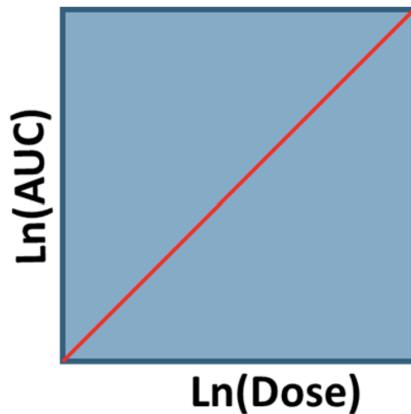
single dose

#### 1.11.4 Dose Proportionality

$$AUC = \frac{F * Dose}{CL}$$

- If Dose and CL are constant,  $AUC \propto F$
- If F and CL are constant,  $AUC \propto Dose$
- If F and Dose are constant,  $AUC \propto \frac{1}{CL}$

### Testing for Dose Proportionality



#### 1.11.5 Bioequivalence

*Test the slope = 1*

*Test the slope = 0*      Average

#### 1.11.6 Food Effects

- This study helps labeling. Important parameters for Food Effect study:
  - Total exposure ( $AUC_{last}, AUC_{\infty}$ )
  - Peak exposure ( $C_{max}$ )
  - Partial exposure (for MR formulations) (pAUC)
  - Time to peak exposure ( $T_{max}$ )
  - Lag-time ( $T_{lag}$ )
  - Terminal elimination half-life ( $t_{1/2}$ )

- Apparent clearance (CL/F)
  - Apparent volume of distribution (V/F)
- If 90% confidence interval for the fed/faasted ratio is wholly contained withing 80-125% then there is no significant food effect.
- 

### **1.11.7 Drug-Drug Interactions**

## **1.12 Create Tables**

### **1.12.1 Create Simple Table**

### **1.12.2 Use Stratification**

### **1.12.3 Add Statistics to Table**

### **1.12.4 Change Column/Sort Order**

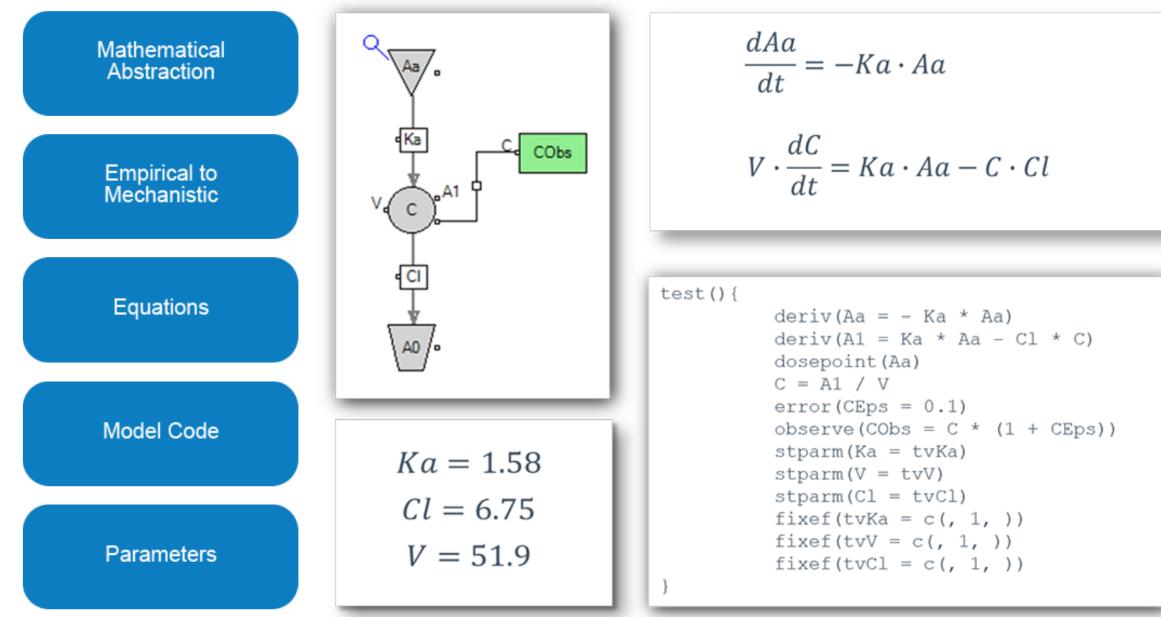
### **1.12.5 Set Precision/Alignment**

### **1.12.6 Change Table Text**

## 2 Introduction to PK Modeling

### 2.0.1 What is a Model

- a mathematical abstraction
- below is a diagram of a typical PK model



The movement of drug through the body is usually much more complicated than depicted in the diagram but even a simple model such as this can mimic the shape of the observed data and allow us to make predictions.

- models can be anywhere from purely empirical to purely mechanistic
- empirical model is used just because it fits the data without drawing too many conclusions about the process that the drug undergoes while being absorbed distributed metabolized and eliminated
- a mechanistic model accounts for many of the processes that the drug is known to undergo
- the model in the diagram is translated into a series of differential equations

- The equations that describe the model are converted into model code in Phoenix
- Parameter values

### 2.0.2 Parameterization

- parameterization refers to the type of parameters that are used in the model
- examples include clearance parameters, micro parameters and macro parameters

let's see how these differ first let's consider

clearance parameters

- the most widely used
- The parameters in this model are the absorption rate constant, the clearance and the volume
- we suggest using clearance parameters when possible because
  - clearances are physiologically relevant and
  - clearance-based models tend to be more stable
  - it is also easy to obtain initial estimates by using parameters from NCA

micro-parameters

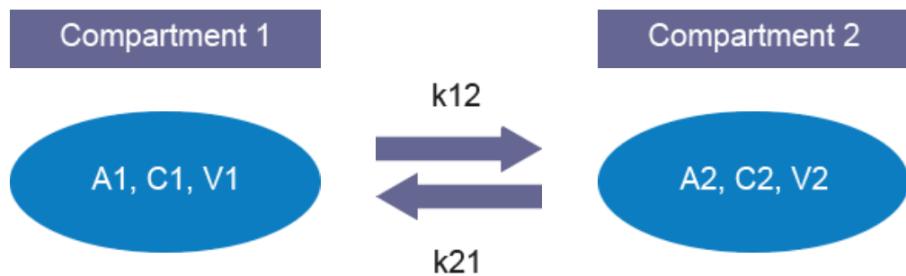
- All the transport is defined in terms of rate constants
- These models are also widely used particularly for more mechanistic
- In the picture model both KA and Ke are rate constants and v is the volume

macro parameter

- These were the first type of parameters to be used in PK modeling
- PK curve is given by an equation that is combination of one or more exponentials
- these parameters are not directly related to the physiology

Clearance parameters and micro-parameters are easily convertible. Let's look at the

Firts, let's consider micro-parameters:



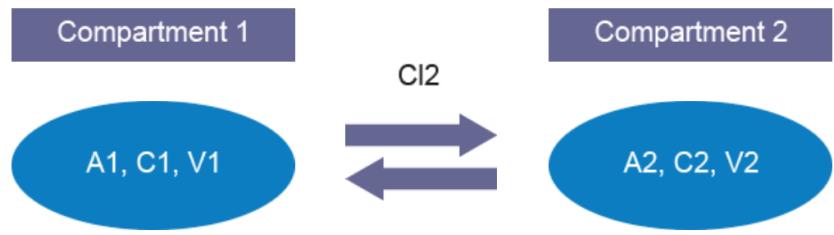
$$\text{Rate} = k * A$$

$$\text{Rate}_{12} = k_{12} * A_1$$

$A_1$  = Amount ( $\mu\text{g}$ )  
 $k_{12}$  = Rate Constant (/h)  
 $\text{Rate}_{12}$  = ( $\mu\text{g}/\text{h}$ )

$$\text{Rate}_{21} = k_{21} * A_2$$

- drug can move in both direction k: rate constants A ;amount of drug in the originative compartment



$$\text{Rate} = Cl * C$$

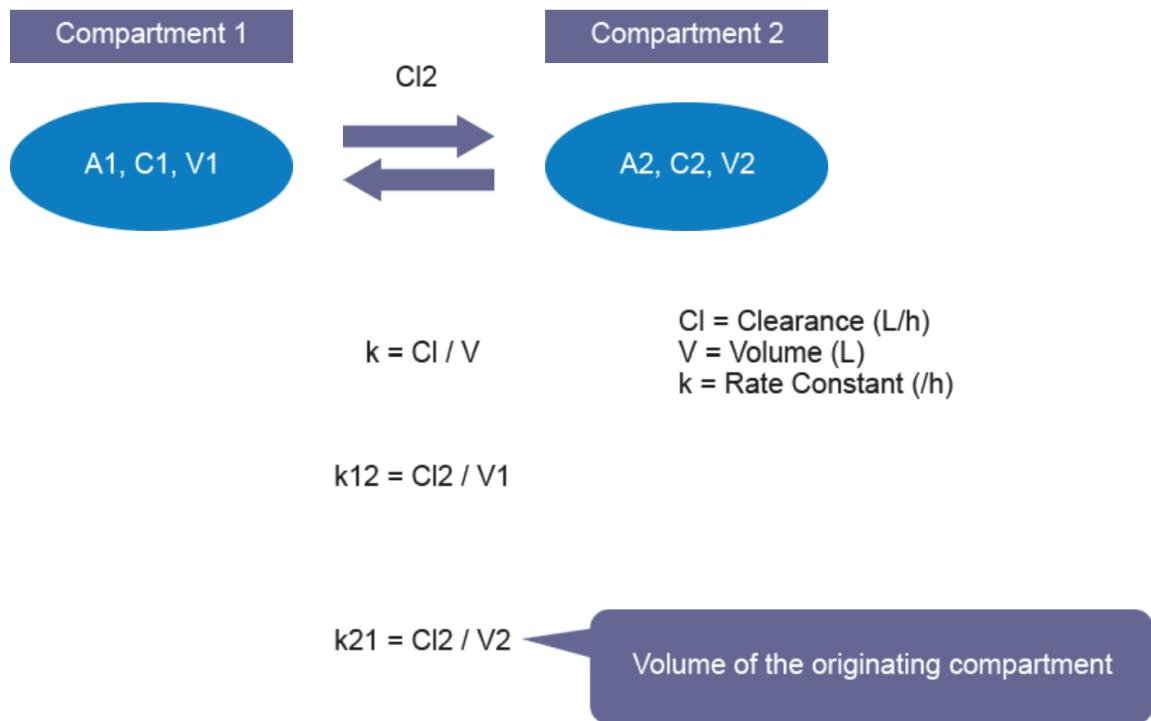
$$\text{Rate}_{12} = Cl_2 * C_1$$

$C_1$  = Concentration ( $\mu\text{g/L}$ )  
 $Cl_2$  = Clearance ( $\text{L/h}$ )  
 $\text{Rate}_{12} = (\mu\text{g/h})$

$$\text{Rate}_{21} = Cl_2 * C_2$$

Next the clearance parameters

Clearance and microcompartment models are usually equivalent and gives similar results. However, clearance models are more commonly used.



### 2.0.3 Administration

the way the drug is administered has a large effect on the shape of the PK curve. three types of administration

#### 1. Extravascular

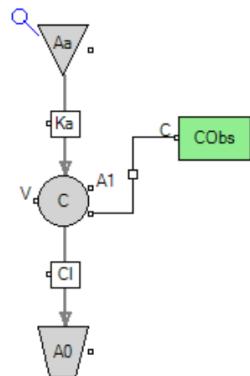
- Oral, subcutaneous, interventional, etc any kind of administration that involves an absorption
- there is a depot compartment that receives the dose
- in Phoenix the dose point is indicated with the blue syringe, The name of the absorption compartment is AA and the absorption rate constant is KA any administration

#### 2. Intravenous (IV infusion or IV bolus)

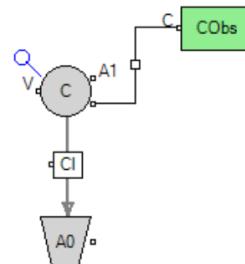
- Delivered at a constant rate for a defined duration or rate
- there is no absorption process and the dose point delivers the drug directly into the central compartment

let's compare the shapes of PK curves resulting from different administration methods here are three simulations all with - a dose of 5,000 micrograms - a volume of 100 liters - a clearance of 20 liters per hour and - an absorption rate constant  $k_a$  of 1 per hour

**Extravascular**



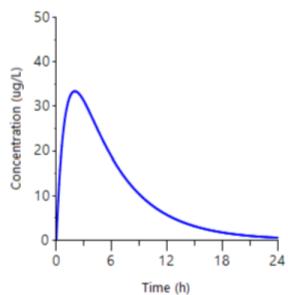
**Intravenous**



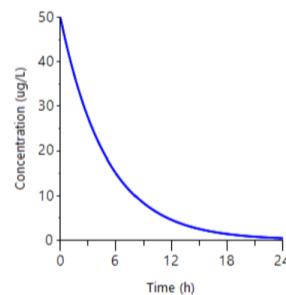
Oral, Subcutaneous,  
Intramuscular, etc.

Bolus or Infusion

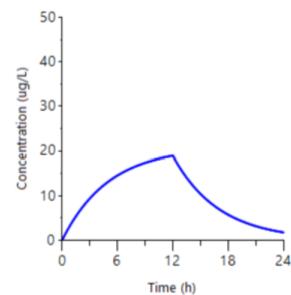
Extravascular



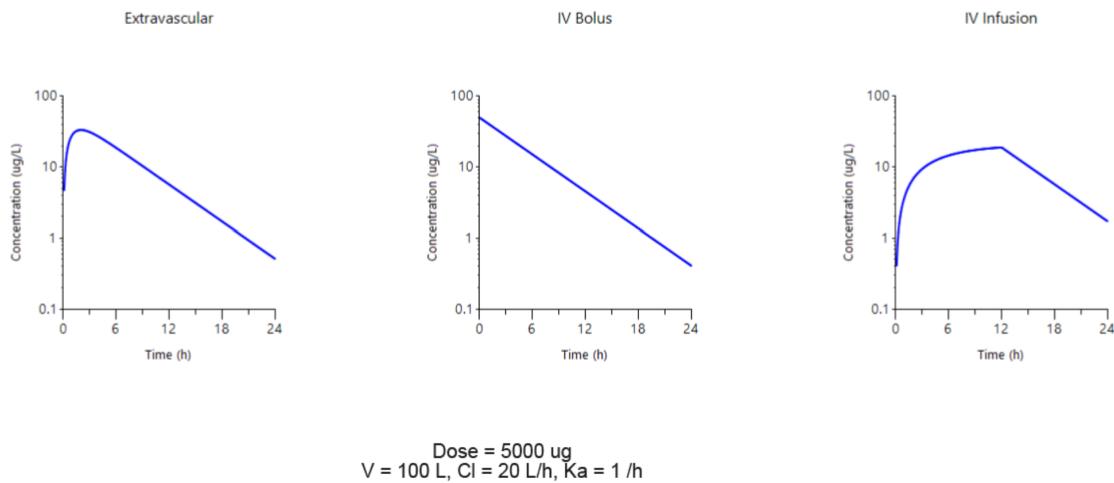
IV Bolus



IV Infusion



Dose = 5000 ug  
 $V = 100 \text{ L}$ ,  $Cl = 20 \text{ L/h}$ ,  $K_a = 1 / \text{h}$



- the elimination phase is linear in all three plots and there is no distribution phase seen

#### 2.0.4 Model structure

- the model structure affects the shape of the pK profile
- three different aspects of model structure
  - number of compartments
  - presence or absence of a time lag
  - saturating elimination

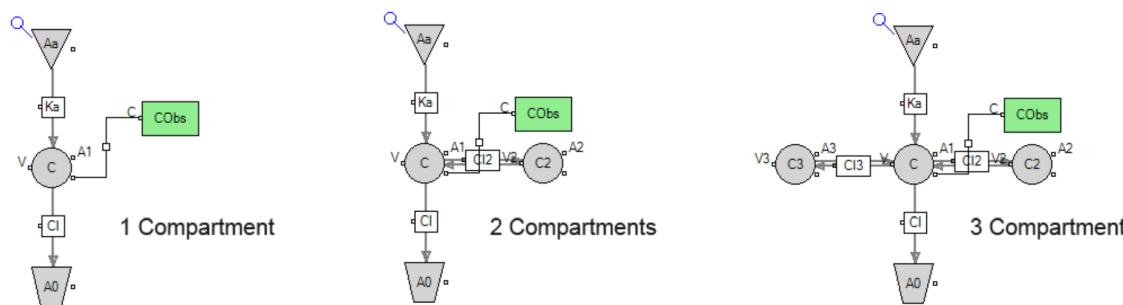
The effect of the number of compartments:

one compartment model is the simplest

- one compartment extravascular model
- has three parameters  $k_a$ ,  $V$  and  $CL$

Two compartment models adds a peripheral compartment which can take up some of the drug  
 - needed when there is a sizable distribution phase - five parameters

three compartments - adds two more parameters  $V3$  and  $CL3$  - The three compartment model is



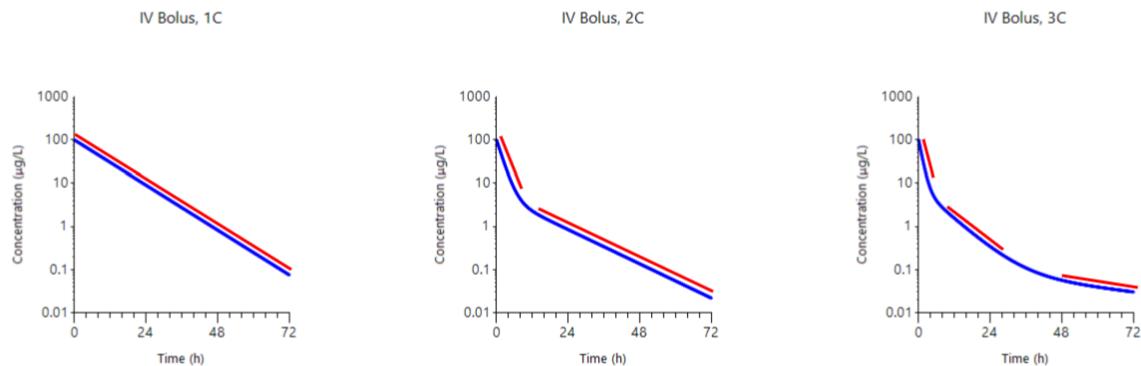
Ka, V, Cl

not used frequently

Ka, V, V2, Cl, Cl2

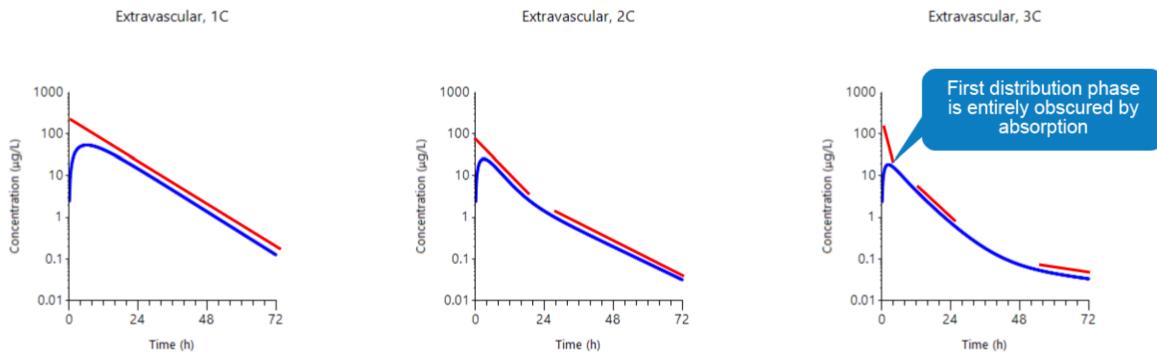
shape but the PK curve

Ka, V, V2, V3, Cl, Cl2, Cl3



- one compartment IV bolus model is just a straight line when plotted on a log concentration axis
- a two compartment model is useful when there is a distribution phase that is different than the elimination phase
- The three compartment model can have three distinct phases
- it will not always be as apparent that there are multiple phases instead of two distinct phases
- we may see a general curvature that blends two or more phases together

corresponding extravascular Administration but



- Early distribution phases can become obscured because of the absorption phase - this is particularly apparent in the three compartment model where the first distribution phase is entirely obscured by the absorption

### Time lag

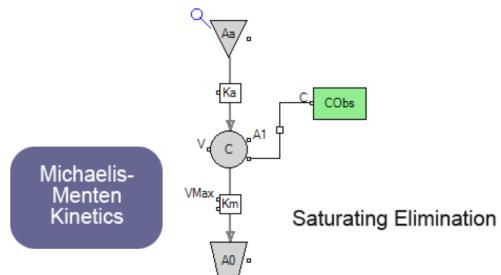
many drugs take some time to show up in systemic circulation and the time lag is a way that we can account for this in our model

on the left is a model with the time lag and on the right is the corresponding model without a time lag T-Lag is a parameter that causes the absorption to be delayed Time lag has the same time units as the time column

- add a time lag to your model if  $t_{max}$  does not fit properly
- The model fit can then adjust both the  $K_A$  and the T-Lag values to obtain and improve fit

### saturation

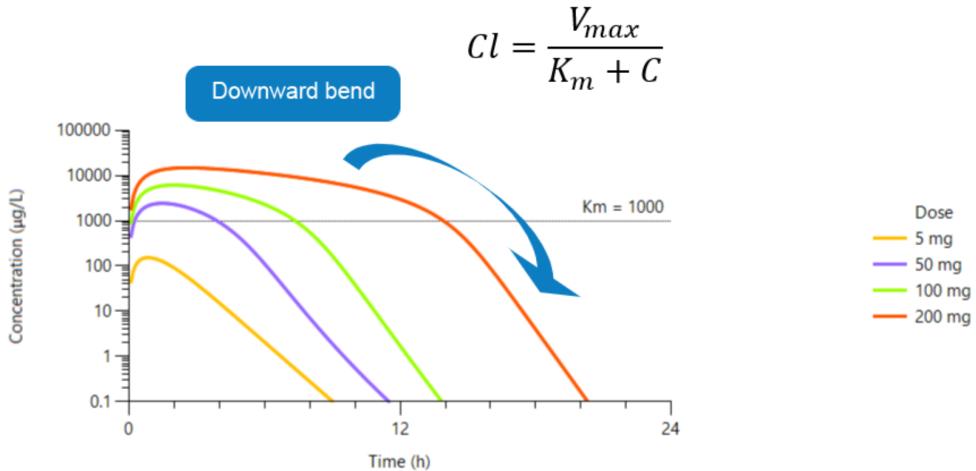
- linear elimination saturation is often referred to as Michaela



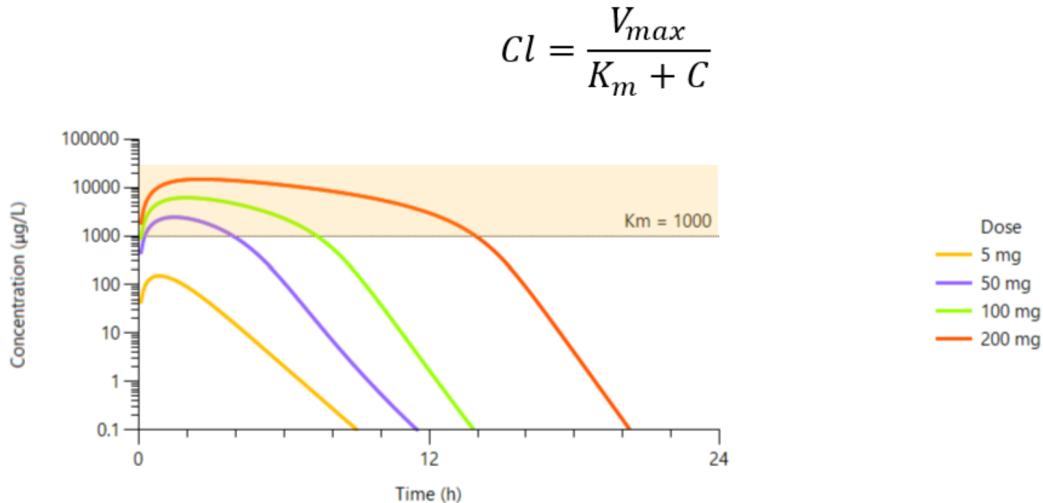
- replaces clearance parameter with  $K_m$  and  $V_{Max}$

$K_a, V, K_m, V_{Max}$

Clearance is no longer constant. Clearance is depended on the concentration. downward bend is characteristics of saturating kinetics saturation increased with higher doses.



- Let's see how this change affects the shape of the PK curve click next to continue



here are simulated curves for a drug that has a Km value of 1,000 in a saturating model clearance becomes the expression  $V_{max}$  over  $km + C$ . this means that clearance depends on the concentration and the clearance is no longer constant notice how different doses have PK curves with dramatically different shapes notice how many of the curves have a downward bend this downward bend is a characteristic of saturating kinetics it may not be observed at lower doses but as the dose increases we may encounter saturation and it is useful to know what it looks like at the lowest dose shown here the yellow curve looks just like a one compartment model with linear kinetics as the dose increases we see more saturation notice how

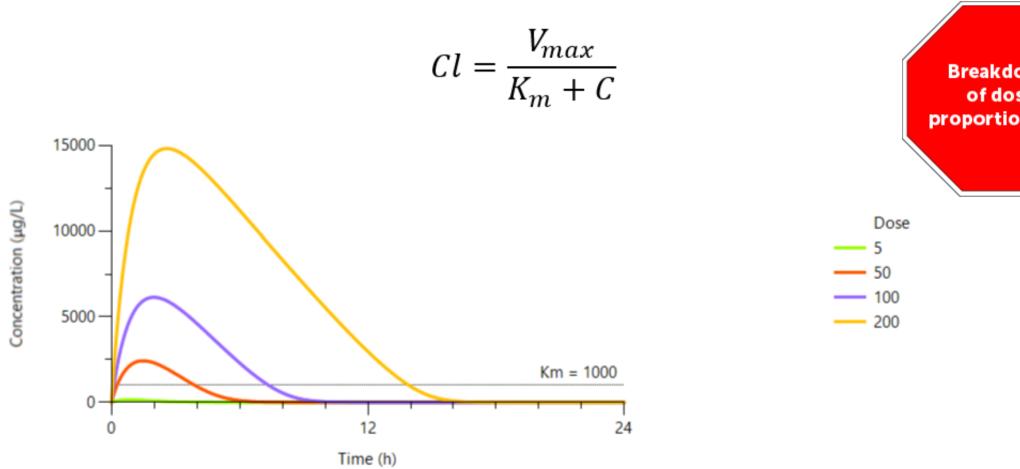
- when the concentration is higher than the Km value the apparent clearance is much lower

and the slopes are much shallower at higher concentrations scale

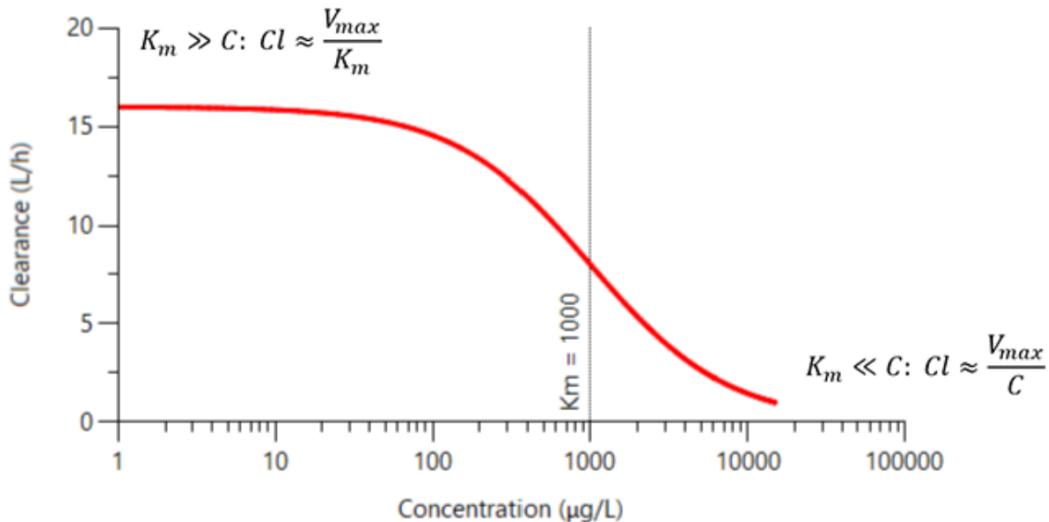
- This breakdown the dose proportionality

Linear scale:

- The increase in AUC is far beyond what we would have predicted under linear kinetics
- In cases were saturation is observed it is important to have data from more than one dose amount so that you can obtain in reliable parameter estimates



$$Cl = \frac{V_{max}}{K_m + C}$$



if we consider the expression for the effective clearance at different concentrations we can consider two extremes when the concentration is much lower than the Km value we do not see any saturation and the clearance is constant clearance over Km at the other extreme when the concentration is much greater than the KM value The clearance reduces to Vmax over c as the concentration increases the clearance becomes progressively smaller at very high concentrations we are overwhelming the elimination pathway usually this happens when an enzyme has a finite capacity to eliminate the drug and we are overloading it you may never need to create a model with saturating elimination but it is good to know when to recognize that saturation

let's recap the section we have seen that the model structure is typically defined by the number of compartments the presence or absence of a time lag and the possibility of saturating elimination These three items can be combined to make a very large number of potential models click next to continue

## 2.0.5 Residual error

Residual error:the difference between the observed and predicted concentrations DV: dependent variable or observed concentration

IPRED: Individual prediction, the predicted concentration

ideal prediction would fall on the line positive residual error negative residual error

$C_{\text{Obs}}(\mu\text{g/L})$

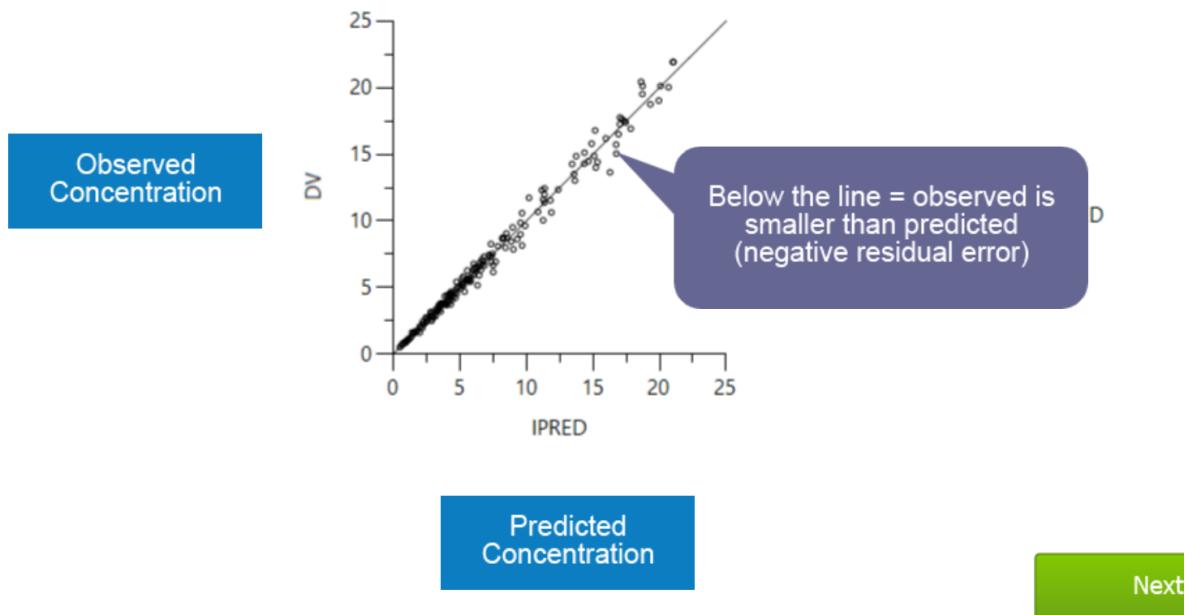
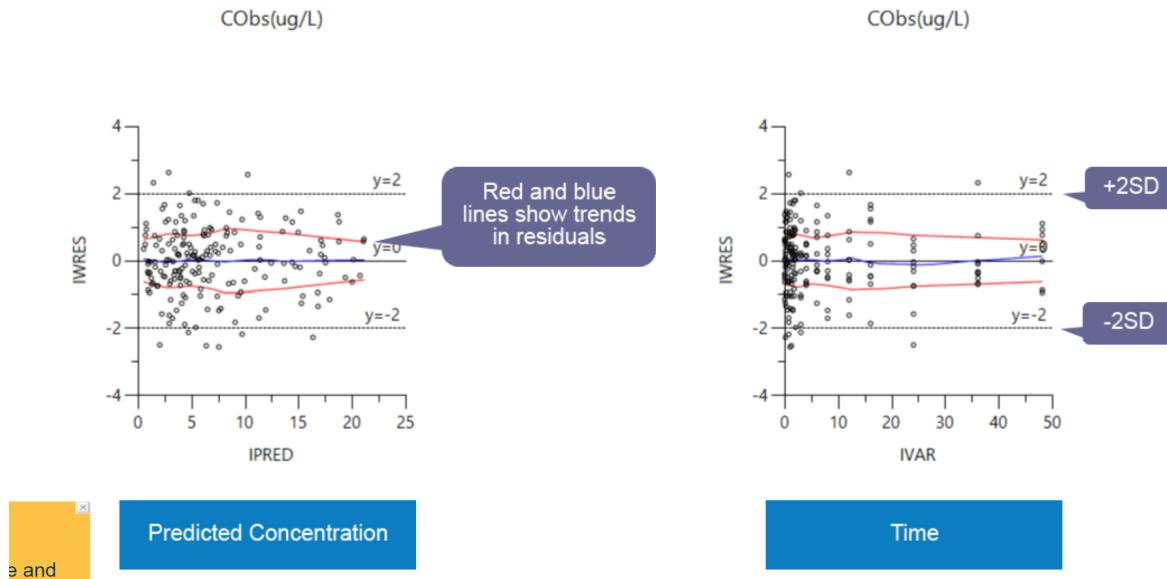


Figure 2.1: residuals

Let's look at another type of plot that is more useful for examining the residuals click next to continue

- These plots show us the residuals on the y-axis with either the predicted concentration or the time on the x-axis
- each point is a residual error
- both plots have the same number of points they're just arranged differently
- The dotted lines represent two standard deviations in the positive and negative directions



Residual worksheet contains the data that was plotted Ires: individual residual, difference between DV and IPRED

different methods for the residual error - additive : assumes that all errors are constant regardless of concentration . In practice we usually find that the error magnitude becomes smaller at smaller concentrations and therefore additive is not often the best choice - multiplicative, assumes that the errors are proportional to the concentration of - additive plus multiplicative: partly constant, partly proportional. at higher concentrations the error magnitude is proportional but at small concentrations the error reaches a threshold and does not decrease any more as the concentration falls

Use multiplicative the initial choice of residual error when building models

Start your modeling using a multiplicative residual error as you are optimizing the structural model - after you have decided on the best structural model then you can start optimizing the residual error model

# 3 Summary

## 3.1 pk model 1

### 3.1.1 Concentrations should be stacked

data format for PK models - observed concentration stacked into a single column - multiple analytes or metabolites concentration should be its own column

	Administration	Time (h)	S1 (ug/L)	S10 (ug/L)	S2 (ug/L)	S3 (ug/L)
1	PO	0	BQL	BQL	BQL	BQL
2	PO	0.125	2.933	2.827	2.893	2.541
3	PO	0.25	6.622	4.331	5.347	4.583
4	PO	0.5	10.04	9.087	9.905	6.509
5	PO	0.75	11.82	9.086	10.33	7.822
6	PO	1	11.96	9.712	10.78	8.52
7	PO	1.25	12.42	10.64	11.49	9.555
8	PO	1.5	11.37	10.25	10.61	8.754
9	PO	1.75	11.72	9.571	9.71	8.487
10	PO	2	10.51	8.425	9.423	8.912
11	PO	3	7.97	8.898	8.448	7.35
12	PO	4	8.338	7.486	7.983	6.384
13	PO	6	5.296	5.581	7.516	5.578
14	PO	8	5.641	4.234	6.539	4.912
15	PO	12	4.503	3.879	5.156	4.017
16	PO	16	4.201	3.409	4.077	3.634
17	PO	24	3.581	2.276	3.278	2.744
18	PO	36	2	1.339	1.807	1.462
19	PO	48	1.207	0.7244	1.174	0.8812

Use Stacker to put concentrations from all subjects in one column

	Administration	Subject	Dose(mg)
1	PO		1
2	PO		1
3	PO		1
4	PO		1
5	PO		1
6	PO		1
7	PO		1
8	PO		1
9	PO		1
10	PO		1

Sort variables

- For multiple PK profiles, one or more sort variables are required.
- Sort variables need to have a value on every row
- In Phoenix text values, blank cells are not a problem
- All non-numeric data is ignored by the model

Sort variable(s)      Time      Concentration

	Administration	Subject	DoseLevel (mg)	Time (h)	Conc (ug/L)	Amount_Oral (ug)
1	PO	1	4	0	BQL	4000
2	PO	1	4	0.125	2.933	
3	PO	1	4	0.25	6.622	
4	PO	1	4	0.5	10.04	
5	PO	1	4	0.75	11.82	
6	PO	1	4	1	11.96	
7	PO	1	4	1.25	12.42	
8	PO	1	4	1.5	11.37	
9	PO	1	4	1.75	11.72	
10	PO	1	4	2	10.51	

- amount oral column has a value at time zero and the rest of the rows are blank. The dose amount is given only on the row that corresponds to a dosing event
- dose level column has a value on every row
- units: unlike NCA the model object does not translate units
- The dose unit should always be the same as the unit in the concentration

And your parameter values keep them the same so that the units will work out properly One more warning the model object allows you to either map the dosing amounts in the main input or the dosing input Make sure that you don't map the dose amount in both places or your administered dose will be twice as large as you intended click next to continue let's recap the section we saw how the model object requires stacked concentrations you should have a single concentration column for each observation second we use sort variables to define the individual PK profiles there's nothing wrong with having more sort variables than you need third we saw how dosing events can be included in the data set remember that these are entered on the row at the time of the dosing event and finally we learned that text values and empty cells are okay in the input and we do not have to do anything to them this completes the section click

# 4 My Notes

## 4.1 Courses

1. (103-OD) Fundamentals of Pharmacokinetics [Conceptual Course]
2. (105-OD) Noncompartmental Data Analysis [Conceptual Course]
3. (122-OD) Introduction to Phoenix WinNonlin (Part 1) - NCA
4. (123-OD) Introduction to Phoenix WinNonlin (Part 2) - Modeling

### 4.1.1 create a new repository on the command line

```
echo "# test" >> README.md
git init
git add README.md
git commit -m "first commit"
git branch -M main
git remote add origin https://github.com/drnazmul/test.git
git push -u origin main
```

### 4.1.2 ...or push an existing repository from the command line

```
git remote add origin https://github.com/drnazmul/test.git
git branch -M main
git push -u origin main
```

After any change made on github repo but not on the local folder, do the following

```
git pull --rebase origin main
git push origin main
```

#### **4.1.3 Publishing Quarto site or book**

Publish from Git Provider

<https://quarto.org/docs/publishing/netlify.html#publish-from-git-provider>

#### **4.1.4 Custom domain on Netlify with Namecheap**

- Go to Namecheap's account, click Manage on the active domain
- on "Name Server" select "Custom DNS" option
- Go to "Domain Settings" of Netlify
- Custom Domain : Options: Edit site name
- Click on "Add custom domain" and add your domain
- Under "primary domain" options, click "Setup Netlify DNS"
- Click verify tab
- Click Add domain tab
- Click Continue
- copy all the four name servers and paste to the DNS server on Namecheap
- Click Done on Netlify
- 

## **4.2 PBPK notes**

<https://www.admescope.com/whats-new/blog/2016/pbpk-what-it-is-for>

<https://www.fda.gov/regulatory-information/search-fda-guidance-documents>

<https://www.boomer.org/>

<https://www.pkpd168.com/>

<https://bebac.at/>

Data: Collection of observations or facts. Can be text, number, audio, video, pics,

- We encounter data 1. purposefully 2. Unintentionally
- Understanding the data we encounter everyday is where the data literacy comes in.

- Data Literacy: how a person interacts with data to make sense of the world around them
- Data literate person:
  - recognize usefulness of the data
  - Interrogate reliability: When, where and how the data was collected?
  - Discover meaning
  - Make decision
  - Communicate findings
  - Do everything ethically

#### **4.2.1 Recognize usefulness of the data**

when you encounter a data: ask: Is this data relevant and useful to me? If so, how?

$$\% \text{ increase} = (\text{final value} - \text{initial value}) / \text{initial value} * 100$$

Questions to ask:

- what's the story the author is trying to make
- What data are they presenting and how are they presenting it?
- What is the agenda behind the information being presented
- how might this data help others to make decisions
- what do you like and what would you do differently?

Data: which is most useful? Which is not relevant?

Make a plan with the questions

Spectacle eyes and curious mind are essential for data literate person

#### **4.3 Courses to take**

- <https://www.coursera.org/specializations/precalculus-data-modelling>
- NONMEM paper Keizer, Karlsson, and Hooker (2013)
- PM and ML paper Keutzer et al. (2022)

## References

- Keizer, R J, M O Karlsson, and A Hooker. 2013. “Modeling and Simulation Workbench for NONMEM: Tutorial on Pirana, PsN, and Xpose.” *CPT: Pharmacometrics & Systems Pharmacology* 2 (6): e50. <https://doi.org/10.1038/psp.2013.24>.
- Keutzer, Lina, Huifang You, Ali Farnoud, Joakim Nyberg, Sebastian G. Wicha, Gareth Maher-Edwards, Georgios Vlasakakis, et al. 2022. “Machine Learning and Pharmacometrics for Prediction of Pharmacokinetic Data: Differences, Similarities and Challenges Illustrated with Rifampicin.” *Pharmaceutics* 14 (8): 1530. <https://doi.org/10.3390/pharmaceutics14081530>.