

## Exercise 10: Built-in Models in DME: Population PK/PD Model with PK Fixed

### Background

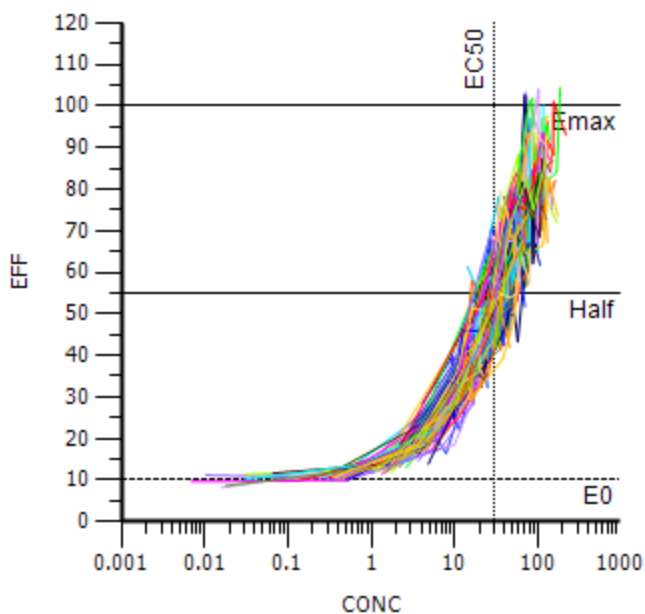
The dataset for this exercise contains simulated observations for 200 subjects.

### Objectives:

- Obtain initial estimates using plotting and NCA
- Fit a Population PK model
- Fit a Population PKPD Model with PK parameters “fixed” or “frozen”
- Understand Results

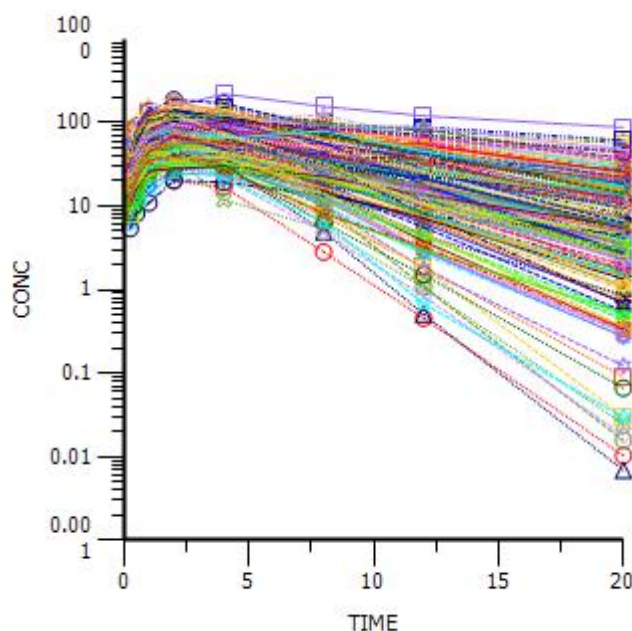
### Part 1a – Exploratory Analysis: Plotting

1. Create a new Project and rename the project, **pkfix\_pd**.
2. Import the dataset ‘**sim3102phx.xls**’.
3. Right-click on the worksheet and select Send To>Plotting>XY Plot. Plot CONC on the x-axis and EFF on the Y axis, grouping by ID. Execute. View the results.
4. Change the scale of the X-axis to logarithmic. From the plot, E0 appears to be 10, EC50 appears to be around 30, and Emax around 100.



5. Right-click on the worksheet and select Send To>Plotting>XY Plot. Plot CONC on the y-axis and TIME on the X axis, grouping by ID. Execute. View the results.

6. Change the scale of the Y-axis to logarithmic. The PK data appear to follow a 1-compartment model with extravascular absorption. Also, the PK concentration data span several orders of magnitude. This suggests a multiplicative residual error model may be appropriate.

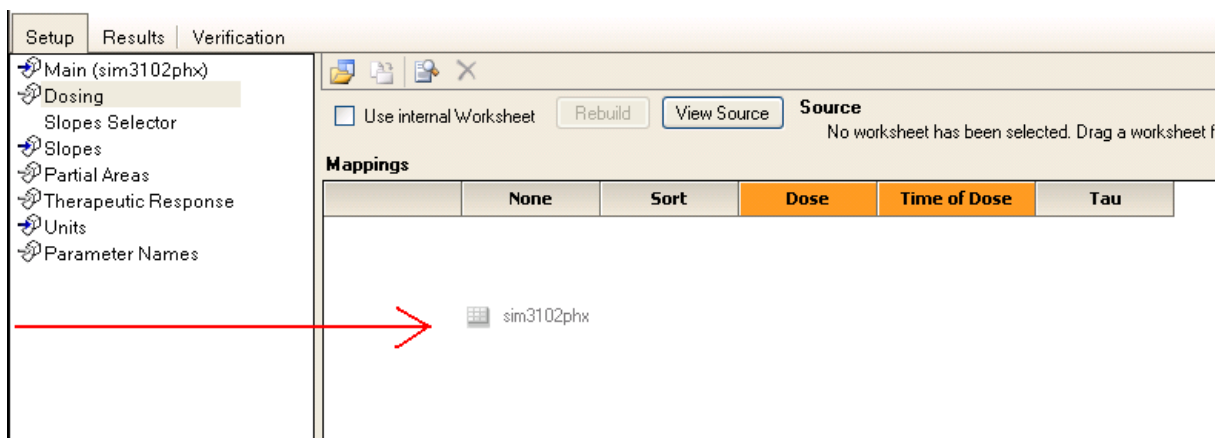


### Part 1b – Exploratory Analysis: NCA to Obtain Initial Estimates

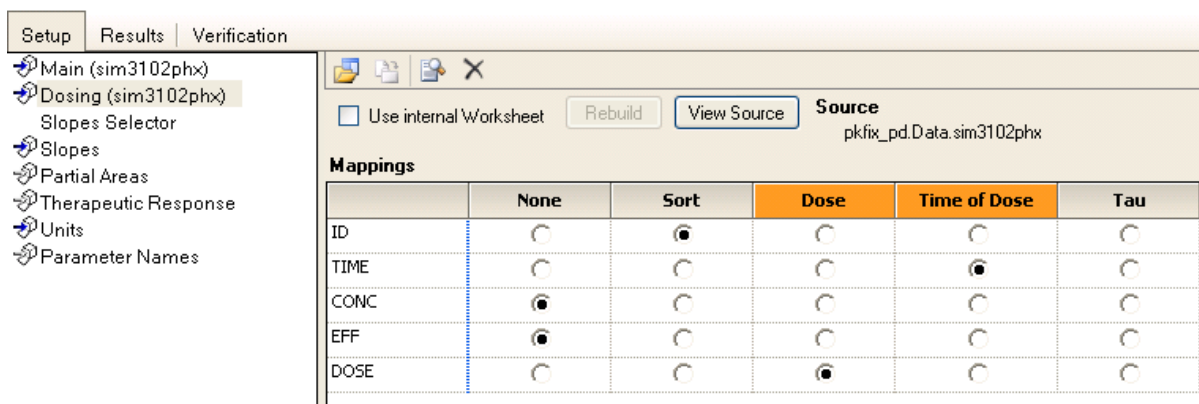
7. Right-click on the worksheet and Send to> NCA and Toolbox> NCA.  
8. Make the following selections.

	None	Sort	Carry	Time	Concentration
ID	<input type="radio"/>	<input checked="" 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"/>
CONC	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
EFF	<input checked="" type="radio"/>	<input 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"/>	<input type="radio"/>

9. Select 'Dosing' in the Setup Tab. Drag the worksheet to the dosing section.

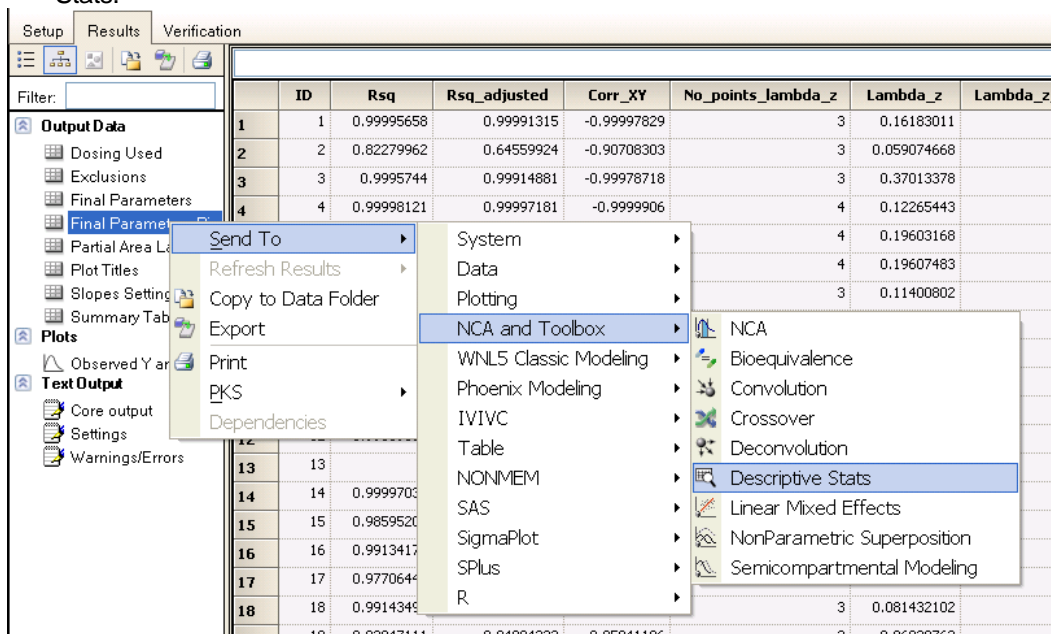


10. Make the following selections.



11. Execute the NCA object.

12. Right-click on the "Final Parameters Pivoted" worksheet and Send To> NCA and Toolbox> Descriptive Stats.



13. Summarize the following variables.

- Lambda\_z
- Vz\_F\_obs
- Cl\_F\_obs
- Vz\_F\_pred
- Cl\_F\_pred

14. Execute the Descriptive Stats object. Initial estimates for V and Ke are 1 and 0.17, respectively.

Setup Results Verification										
Filter:										
Output Data										
Statistics										
Text Output										
Settings										
Variable	N	NMiss	NObs	Mean	SD	SE	Variance	Min		
1 Cl_F_obs	195	5	200	0.16869435	0.1190977	0.0085287633	0.014184262	0.020077527		
2 Cl_F_pred	195	5	200	0.16866492	0.11914661	0.008532266	0.014195915	0.020738289		
3 Lambda_z	195	5	200	0.16760659	0.094126407	0.006740532	0.0088597806	0.01771128		
4 Vz_F_obs	195	5	200	1.0362653	0.50185848	0.035938832	0.25186193	0.31647184		
5 Vz_F_pred	195	5	200	1.0362081	0.50350808	0.036056962	0.25352039	0.31677626		

## Part 2 – Population PK Base Model

15. Right-click on the worksheet and Send To>Phoenix Modeling>Phoenix Model.

16. Set up the model mappings and Built-in options as shown below. The options are: PK model, Micro, Parameterization, Extravascular, 1 compartment, Multiplicative Residual Error. DOSE is mapped to Aa, and CONC is mapped to CObs.

Setup Results Verification

Main (sim3102phx)

Model

Dosing

Parameters

Parameters.Mapping

Source: pkfix\_pd Data.sim3102phx

Mappings

	None	Sort	ID	Aa	Time	CObs
ID	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
TIME	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
CONC	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
EFF	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
DOSE	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

Mapping Output Sort Order

Population? ☒ Structure Parameters Input Options Initial Estimates Run Options Model Text Plots no warnings

Type: PK

Parameterization: Micro

Absorption: Extravascular

Num Compartments: 1

Parameters: Ka V Ke

Statements: cfmicro(A1, Ke, first = (Aa = Ka))  
dosepoint(Aa)  
C = A1 / V  
error(CEps = 1)  
observe(CObs = C \* (1 + CEps))

☐ tlag? ☐ Ka = Ke? ☐ Elim. Cpt.?

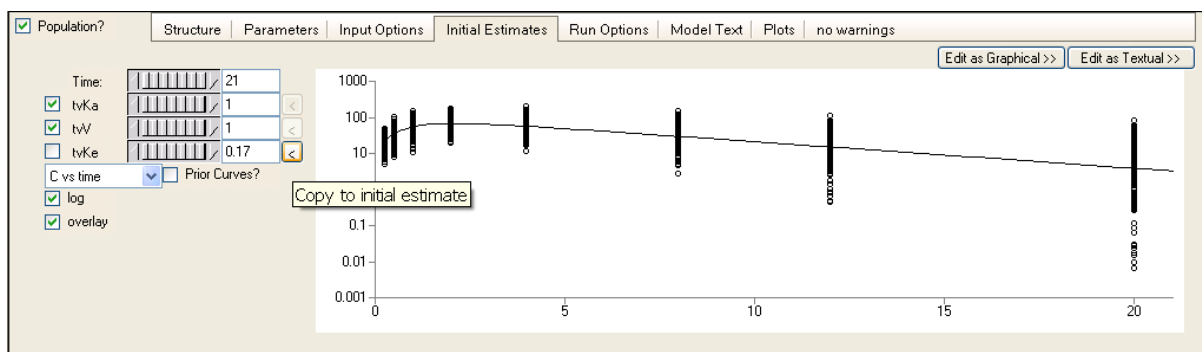
☒ Closed form?

☐ Infusions possible?

Residual Error: C CObs CEps = Multiplicative ☐ BQL?

Stdev: 1

17. Click on the Initial Estimates Tab. Select the “log” and “overlay” checkboxes. Move the sliders to obtain initial estimates and/or use the initial estimates obtained from NCA. Click on the left arrow button (“<”) when finished to use the number displayed in the field as the initial estimate. The button should turn grey after clicking on it.

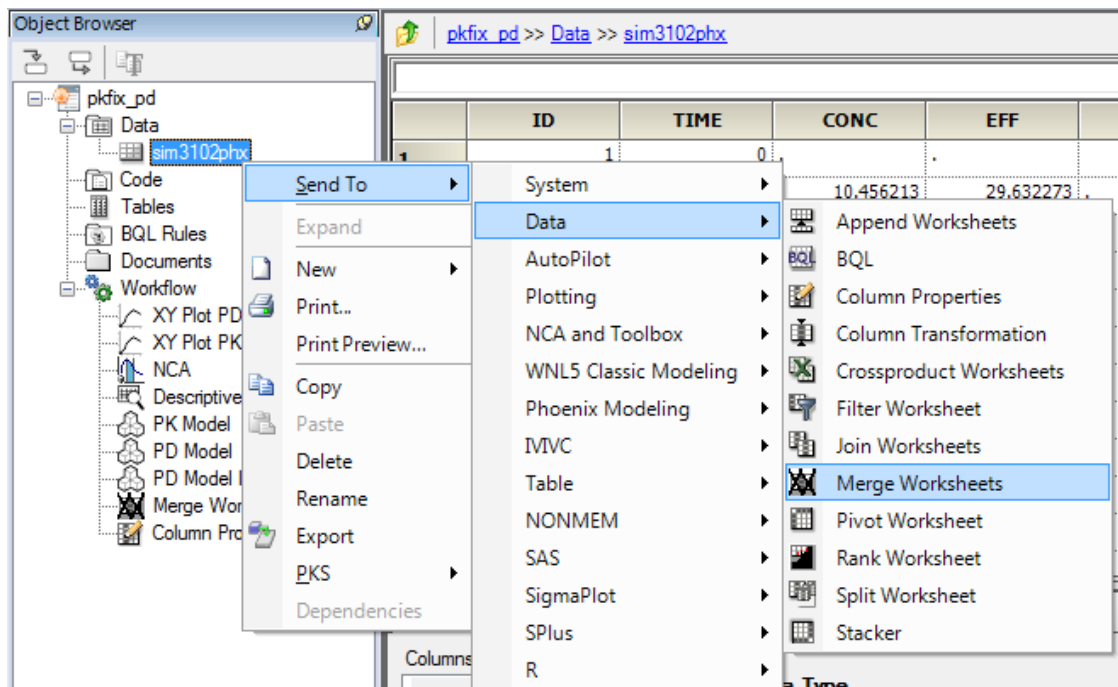


18. Go to the Run Options tab. Click “Add Table”. Click “Structural Parameter”. A table of the individual PK parameters will be outputted in a table called Table01 in the results tab after the model is executed.

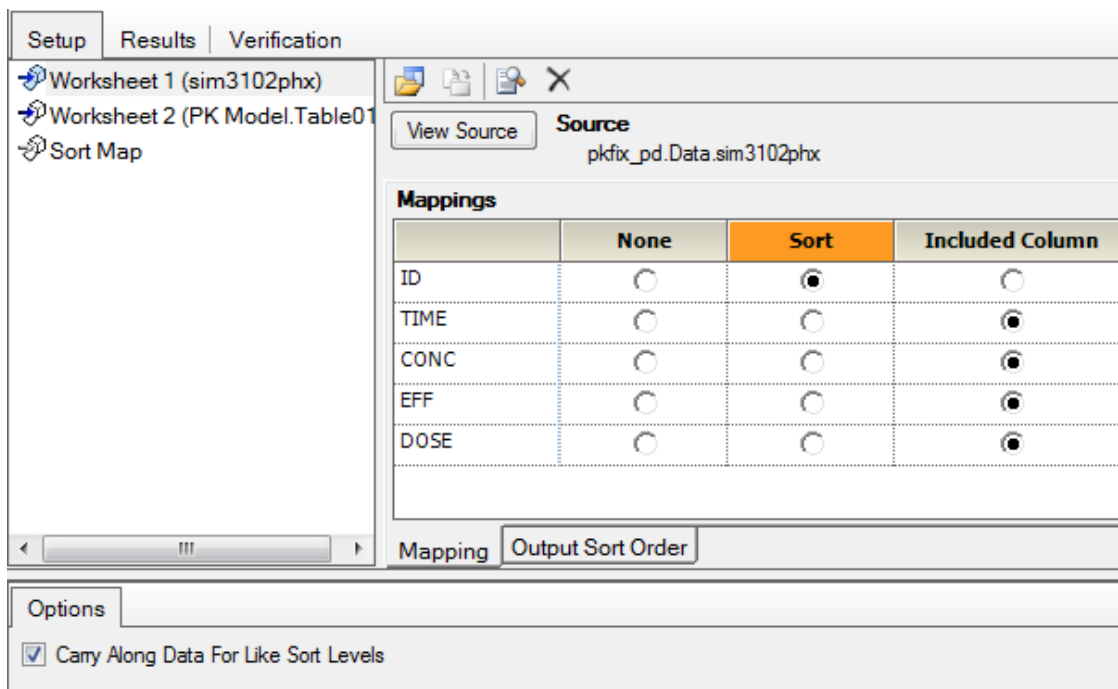
19. Execute the PK model.

### Part 3 – Population PD Base Model with PK Frozen

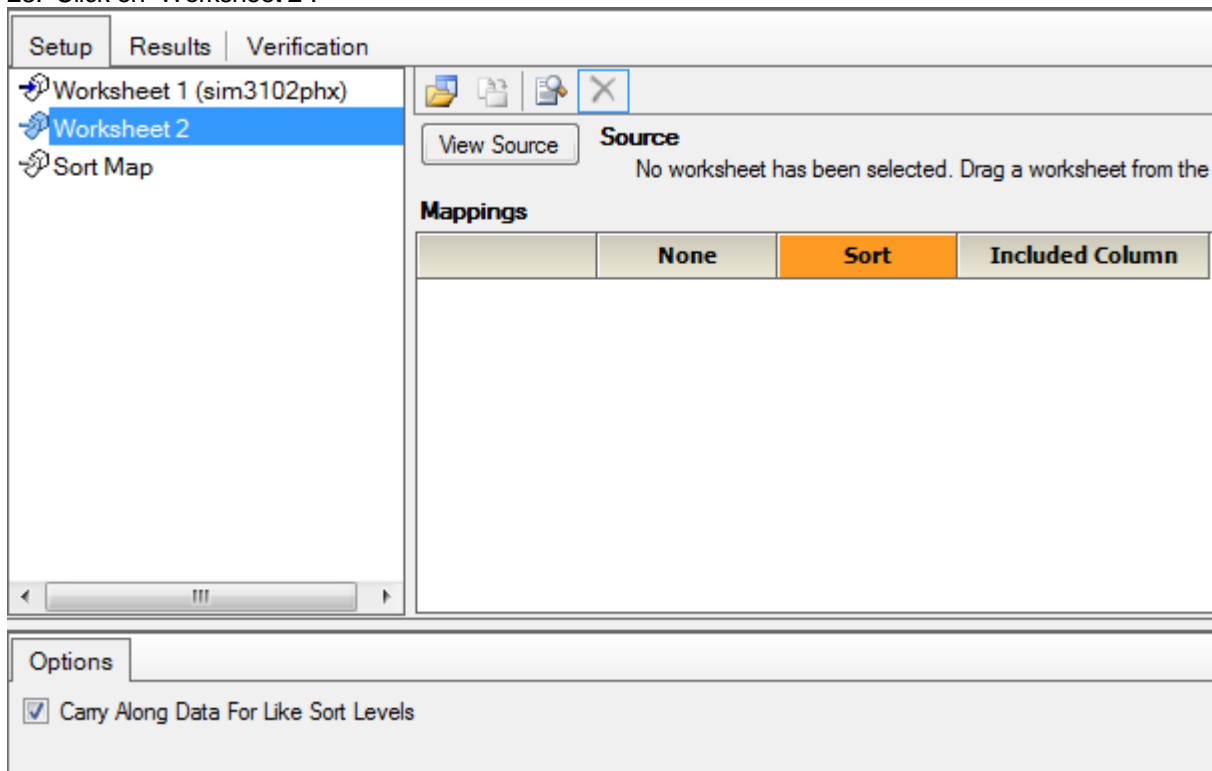
20. In the Results tab of the PK model, verify that the results look reasonable (thetas have low CV%, estimates are plausible, etc). If not, check the model settings and initial estimates and re-execute.
21. In the Object Browser, right-click on the dataset “sim3102phx” and Send To>Data>Merge Worksheets.



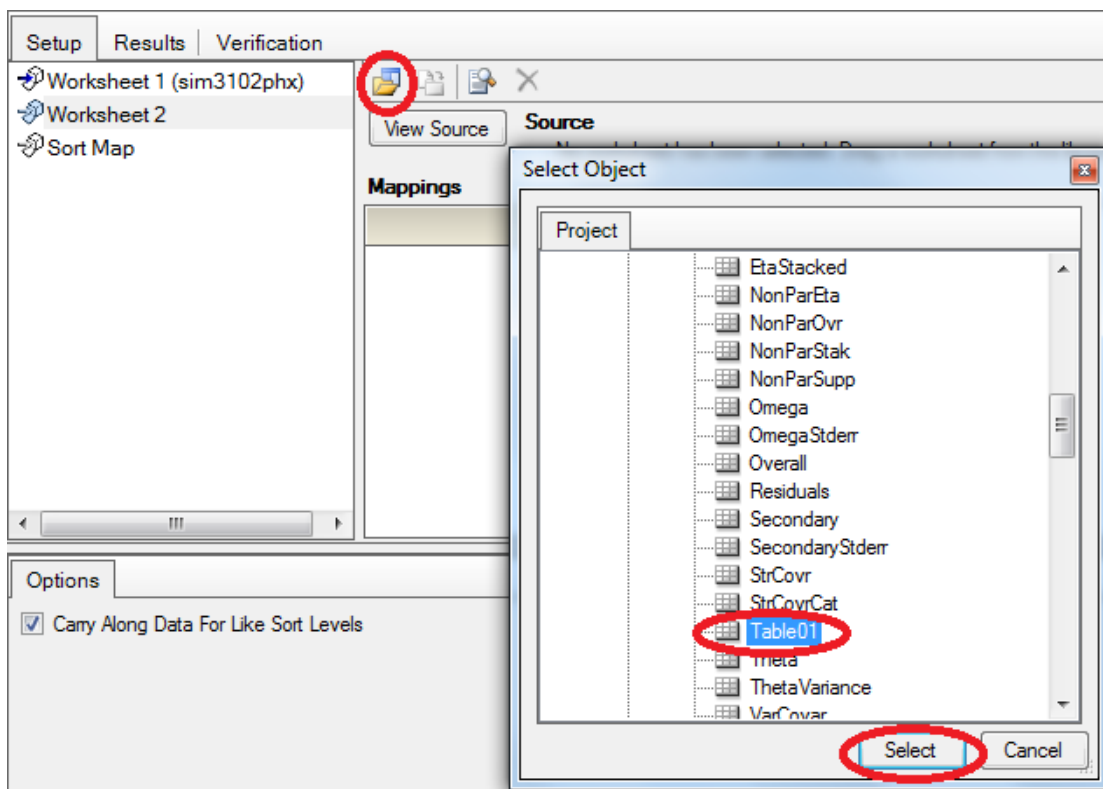
22. For Worksheet 1, Sort by ID and Include everything else.



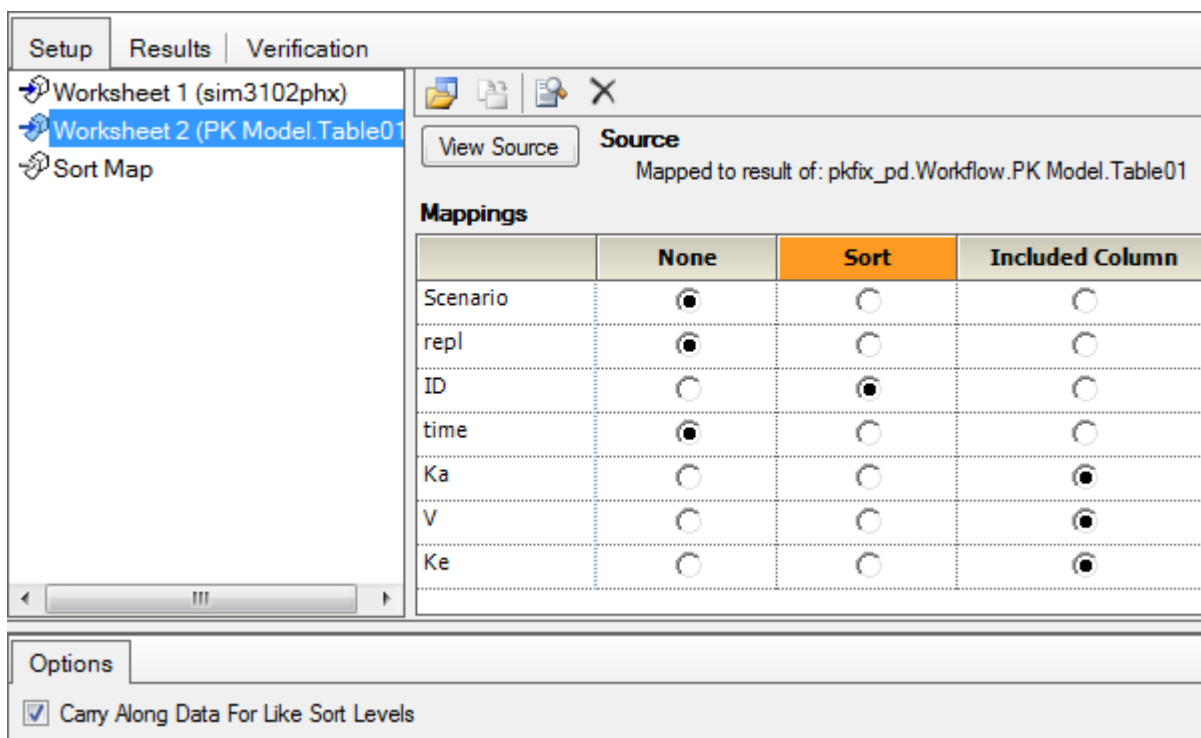
23. Click on "Worksheet 2".



24. Click the "Select Source" button and select Table01 from the PK model.

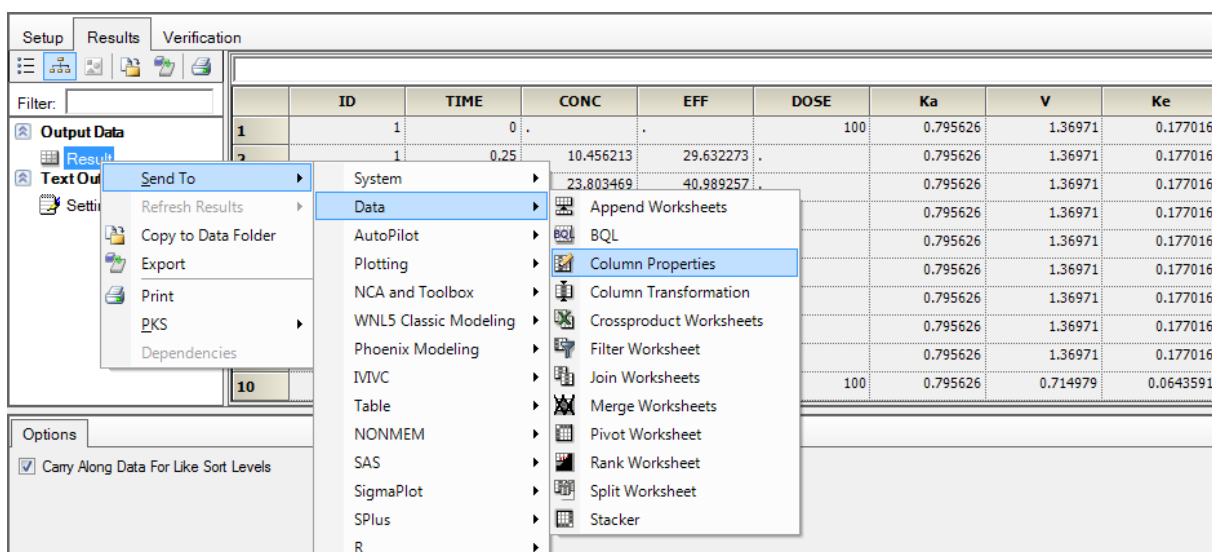


25. For Worksheet 2, Sort by ID and Include Ka, V, and Ke.



26. Execute the Merge Worksheets object.

27. Right-click on the resulting worksheet and Send To> Data>Column Properties.





28. Rename the columns “Ka”, “V”, and “Ke” to “Kaf”, “Vf”, and “Kef” using the Options panel. (Hint: Use “Enter” to set the new names or else they might not register as entered.)

The screenshot shows the 'Options' panel in Phoenix WinNonlin. The 'Old Column (Unit) => New Column (Unit)' list on the left contains the following entries:

- ID => ID [Double]
- TIME => TIME [Double]
- CONC => CONC [String]
- EFF => EFF [String]
- DOSE => DOSE [String]
- Ka => Kaf [Double]
- V => Vf [Double]
- Ke => Kef [Double]

The 'New Column Name' field is set to 'Kef'. The 'New Unit' is set to '<none>' with a 'Convert' checkbox. The 'New Data Type' is set to 'Numeric'.

	ID	TIME	CONC	EFF	DOSE	Kaf	Vf	Kef
1	1	0	.	.	100	0.795626	1.36971	0.177016
2	1	0.25	10.456213	29.632273	.	0.795626	1.36971	0.177016
3	1	0.5	23.803469	40.989257	.	0.795626	1.36971	0.177016
4	1	1	42.090574	49.779381	.	0.795626	1.36971	0.177016
5	1	2	48.252579	55.837319	.	0.795626	1.36971	0.177016
6	1	4	45.250264	44.868387	.	0.795626	1.36971	0.177016
7	1	8	20.517478	53.234272	.	0.795626	1.36971	0.177016
8	1	12	10.608362	32.247845	.	0.795626	1.36971	0.177016
9	1	20	2.935427	15.502231	.	0.795626	1.36971	0.177016
10	2	0	.	.	100	0.795626	0.714979	0.0643591

29. Execute the Column Properties object.  
 30. Copy/Paste the PK model. Renamed the copied model to “PD model Ind PK fixed”.  
 31. Click the “Select Source” button, and select the result from the Column Properties object as the data input for the PD model.

The screenshot shows the 'Object Browser' on the left and the 'Select Object' dialog on the right. The 'Object Browser' shows a project named 'pkfix\_pd' with a 'Workflow' containing a 'PD Model Ind PK fixed' object. The 'Select Object' dialog shows a tree view of the project structure. The 'Worksheet' object is selected, and the 'Select' button is highlighted.

32. Click on the “Structure” Tab at the bottom, and click on the “Setup” Tab at the top. Change the model type to “PK/Emax” and select “Freeze PK” and “Baseline”. Map EFF to EObs.

Setup Results Verification

Main (sim3102phx)

Model

Dosing

Parameters

Parameters.Mapping

View Source Source

pkfix\_pd.Data.sim3102phx

	None	Sort	ID	Aa	Time	EObs
ID	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
TIME	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>
CONC	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
EFF	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>
DOSE	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input checked="" type="radio"/>	<input type="radio"/>	<input type="radio"/>

Mapping Output Sort Order

Population? Structure Parameters Input Options Initial Estimates Run Options Model Text Plots no warnings

Type: PK/Emax

Parameterization: Absorption: Micro Extravascular Num Compartments: 1

Parameters: Statements:

Ka clMicro(A1, Ke, first = (Aa = Ka))

V dosepoint(Aa)

Ke C = A1 / V

EC50 E = E0 + Emax \* C / (EC50 + C)

E0 error(EEps = 1)

Emax observe(EObs = E + EEps)

Emax: Baseline Inhibitory Sigmoid

Fractional Freeze

Residual Error:

E EObs EEps = Additive BQL?

Sidev: 1 8.42249 Accept

33. In the Parameters Tab>Structural Tab, click “Add From Unused”. Select “Kaf”, “Vf”, and “Kef”. Click “Add”. Click “Yes” for a “Kaf” effect on “Ka”, etc, until effects are added for Ka, V, and Ke.

Population? Structure Parameters Input Options Initial Estimates Run Options Model Text Plots no warnings

Structural Covar. Type Fixed Effects Random Effects Secondary Scenarios

SParm	Style	Fixef	Ran	Ranef	Code
Ka	Product*exp(et)	tvKa	<input type="checkbox"/>		$Ka = tvKa * Kaf^{dKadKaf}$
V	Product*exp(et)	tvV	<input checked="" type="checkbox"/>		$V = tvV * Vf^{dVdVf}$
Ke	Product*exp(et)	tvKe	<input checked="" type="checkbox"/>		$Ke = tvKe * Kef^{dKedKef}$
EC50	Product*exp(et)	tvEC50	<input checked="" type="checkbox"/>	nEC50	$EC50 = tvEC50 * exp(nEC50)$
E0	Product*exp(et)	tvE0	<input checked="" type="checkbox"/>	nE0	$E0 = tvE0 * exp(nE0)$
Emax	Product*exp(et)	tvEmax	<input checked="" type="checkbox"/>	nEmax	$Emax = tvEmax * exp(nEmax)$

Covariate	Center	Pos?	Direction	Ka	V	Ke	EC50	E0
x Kaf		<input checked="" type="checkbox"/>	Backward	Yes	No	No	No	No
x Vf		<input checked="" type="checkbox"/>	Backward	No	Yes	No	No	No
x Kef		<input checked="" type="checkbox"/>	Backward	No	No	Yes	No	No

Add Covariate

Add From Unused

34. Select the Fixed Effects Tab. Enter initial estimates for the PD model as shown below. Freeze the PK parameters to 1 (Note: Parameters are frozen if the “freeze” check box is greyed out).

Population? <input checked="" type="checkbox"/>							
Structure Parameters Input Options Initial Estimates Run Options							
Structural	Covar. Type	Fixed Effects		Random Effects	Secondary	Scenarios	
Fixef	Initial	Lower *	Upper *	Freeze	Estimate	Units *	(*options)
tvKa	1			<input type="checkbox"/>	1	Accept	
tvV	1			<input type="checkbox"/>	1	Accept	
tvKe	1			<input type="checkbox"/>	1	Accept	
tvEC50	35			<input type="checkbox"/>	40.7002	Accept	
tvE0	10			<input type="checkbox"/>	10.0743	Accept	
tvEmax	100			<input type="checkbox"/>	99.6171	Accept	
dKadKaf	1			<input checked="" type="checkbox"/>	1	Accept	
dVdVf	1			<input checked="" type="checkbox"/>	1	Accept	
dKedKef	1			<input checked="" type="checkbox"/>	1	Accept	

Accept All

35. Execute the model object and view the results.

## Part 4 – Covariance Model

36. Look at the Omega Worksheet and note the high shrinkage values for several of the parameters. Click on the Parameters Tab>Structural Tab. Remove the random effects for the parameters with the highest shrinkage values, one at a time (if time permits), executing the model and viewing the results until all random effects left in the model have fairly low shrinkage values (less than 0.3 or 0.4).
37. Save the project and continue on to the next exercise without closing.