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

Background

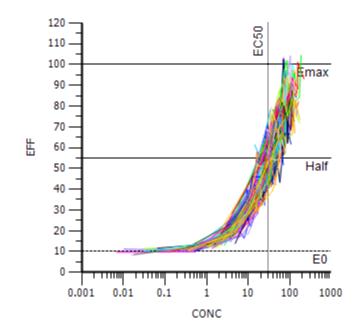
The dataset for this exercise contains simulated observations for 200 subjects.

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

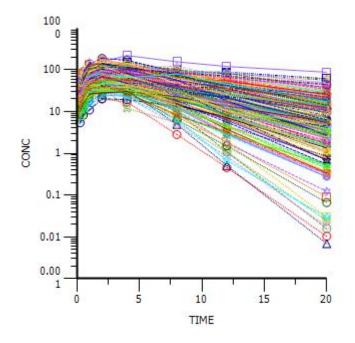
Part 1a – Exploratory Analysis: Plotting

- 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.

 Main (sim 3102phx) Dosing (sim 3102phx) Slopes Selector Slopes 	View Source	pkfix_pd.Data.sim3102phx								
Partial Areas	Mappings									
PTherapeutic Response		None	Sort	Carry	Time	Concentration				
∲Units - 의口 · · · ·	ID	0	۲	0	0	0				
Parameter Names	TIME	0	0	0	6	0				
	CONC	0	0	0	0	•				
	EFF	•	0	0	0	0				
	DOSE	<u> </u>	~	~	~	~				

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

Phoenix WinNonlin NLME Connect Version 1.2.1 Hands-on Training Materials

Main (sim3102phx)	🛃 🔛 🕒	\times				
② <mark>Dosing</mark> Slopes Selector 秒Slopes	🔲 Use interna	Worksheet Reb	uild View So		orksheet has been selec	ted. Drag a workshi
♥ Slopes Partial Areas	Mappings					
P Therapeutic Response		None	Sort	Dose	Time of Dose	Tau
∲Units						
Parameter Names						
		💷 sim3102phx				
		and other print				

10. Make the following selections.

わAain (sim3102phx) わosing (sim3102phx) Slopes Selector わSlopes のPartial Areas	Use intern	Use internal Worksheet Rebuild View Source pkfix_pd.Data.sim3102phx Mappings									
P Therapeutic Response		None	Sort	Dose	Time of Dose	Tau					
∲Units	ID	0	۲	0	0	0					
🖗 Parameter Names	TIME	0	0	0	۲	0					
	CONC	6	0	0	0	0					
	EFF	6	0	0	0	0					
	DOSE	\wedge	\sim	<u> </u>	\sim	~					

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

臣 🚠 🗵 📴 🔭 (Filter:		ID	Rsq	Rsq_adjusted	Corr_XY	No_p	oints_lambda_z	Lambda_z	Lambda_z
🖄 Output Data	1	1	0.99995658	0.99991315	-0.99997829		3	0.16183011	
💷 Dosing Used	2	2	0.82279962	0.64559924	-0.90708303		3	0.059074668	
💷 Exclusions	3	3	0.9995744	0.99914881	-0.99978718		3	0.37013378	
🛄 Final Parameters	4	4	0.99998121	0.99997181	-0.9999906		4	0.12265443	
🕮 Final Paramet 🎟 Partial Area La	Send	То	•	System		•	4	0.19603168	
Plot Titles	Refre	sh Result	s ▶	Data		•	4	0.19607483	
💷 Slopes Setting 📭	Copy	to Data I	Folder	Plotting		•	3	0.11400802	
💷 Summary Tab 🛃	Expor			NCA and Too	box	•	NCA		
N Observed Y ar 🛃	Print			WNL5 Classic	: Modeling	r 🛀	Bioequivalence		
Text Output	PKS		•	Phoenix Mod	eling	F 35	Convolution		
📑 Core output	-	ndencies		IVIVC	Ŭ.	F 36	Crossover		
☑ Settings ☑ Warnings/Errors	14			Table		2	Deconvolution		
armings/Errors	13			NONMEM			Descriptive Sta	ats	
	14		0.9999703	SAS			Linear Mixed E	ffects	
	15		0.9859520	SigmaPlot		• 🙀	NonParametric	: Superpositio	n
	16		0.9913417	SPlus			Semicompartm		
	17		0.9770644	R			•		'a
	18	18	0.9914349				3	0.081432102	
		10	0 02047111	n 94004222	-0 05041186		3	0.06830763	

- 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.

🗄 🚠 🗵 🎦 😚	3									
Filter:		Variable	N	NMiss	NObs	Mean	SD	SE	Variance	Min
🖄 Output Data	1	Cl_F_obs	195	5	200	0.16869435	0.1190977	0.0085287633	0.014184262	0.020077527
Statistics	2	Cl_F_pred	195	5	200	0.16866492	0.11914661	0.008532266	0.014195915	0.020738289
Text Output	3	Lambda_z	195	5	200	0.16760659	0.094126407	0.006740532	0.0088597806	0.01771128
🍠 Settings	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 愛Dosing 愛Parameters	View Source S	ource pkfix_pd.Data.si	im3102phx					
🌮 Parameters. Mapping	Mappings	None	Sort	ID	Aa	Time	CObs	
	ID	O			Ma	0	CODS C	
	TIME	0	0	0	0	6	0	
	CONC	0	0		0	0	6	
	EFF		0		0	0	0	
	DOSE	0	0	0	6	0	0	
		0	0					
Population? Structure		ut Sort Order						
	Parameters Inpu	it Options Initi	lai Estimates		Viodel Text Plo	ts no warning		
Туре: РК 🔽					Set WNL Model		Edit as Gra	aphical >> Edit as Textual >>
Parameterization: Absorption:	Num Compartm			tements:				
Micro 💌 Extravascular	✓ 1	🔽 Ka		icro(A1, Ke, first = (Aa	= Ka))			
tlag? Ka = Ke ?	🔲 Elim. Cpt.?	V		epoint(Aa)				
Closed form?		Ke		A1 / V				
Infusions possible?				r(CEps = 1)				
Residual Error:			obs	erve(CObs = C * (1 +)	(Eps))			
C CObs CEps = Multiplicativ v Stdev: 1	BQL?							

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.</p>

Population?	Structure Parameters	Input Options	Initial Estimates	Run Options	Model Text	Plots no warnings		
							Edit as Graphical >>	Edit as Textual >>
Time:	1 / 21	1000						
🗹 tvKa		100- 🔒 🗎	1 1		1	8		
✓ tvV		11-	1 1-					
C vs time	0.17 Curves?	10-	•					
C vs time ✓ log		y to initial estim	nate		•			
verlay	·	0.1-				Ū		8
								8
		0.01 -						8
		0.001		5	1	0	15	20
		0		0		U	15	20

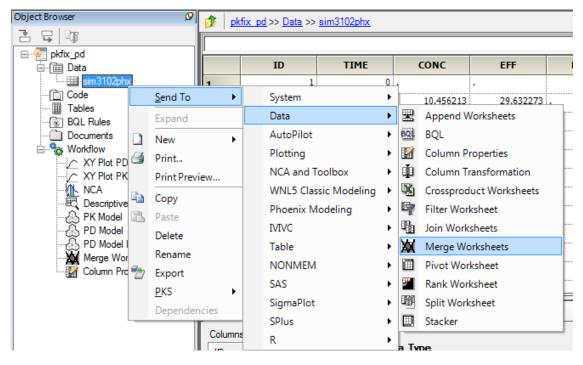
18. Go to the Run Options tab. Click "Add Table". Click "Structural Parameter". A table of the individual PK parameters will be outputted in a table called Table01 in the results tab after the model is executed.

Population?	Structure	Parameters	Input Options	Initial Estimates	Run Optio	ns Model Tex	Plots	no warnin	gs		
										Edit as Graphical >>	Edit as Textual >>
Method: FOCE L-B	-	Stderr:	Central Diff 💌	Run Mode	Ta	able01 🗴 🗹 📔					
Lindstrom-Bates: Bes		Sandwich?		Simple		Add Table					
Additive or Log-additi	ive error	Confidence Let	vel %	Scenarios		Structural Pa	rameter				
N Iter: 1000		95	5	Cov. Srch. Step	pwise Ti	ìmes:					
NonParametric		PCWRES?		Cov. Srch. Sho	otgun W	Vhen covr set:					
Sort Input?		Advanced >	»>	Bootstrap	W	Vhen dose:					
Use MPI?				Profile	W	Vhen observe:					
Max ODE: matrix e	-			Sim. / Pred. Cł	heck Va	ariables: Ka.	√.Ke				
Synthetic Gradien	nts?					TAD IF	ES 🗌	Weight	IWRES		
Properties Informa	ation Histor	у									

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.

Setup Results Verification								
Worksheet 1 (sim3102phx)	🛃 🖹 🔒 🕽	K						
	1 View Source	View Source pkfix_pd.Data.sim3102phx						
	Mappings							
		None	Sort	Included Column				
	ID	0	۲	0				
	TIME	0	0	۲				
	CONC	0	0	۲				
	EFF	0	0	۲				
	DOSE	0	0	۲				
		<u>.</u>						
۰ III • •	Mapping Outp	ut Sort Order						
Options								
Carry Along Data For Like Sort Leve	els							

23. Click on "Worksheet 2".

Setup Results Verification				
Worksheet 1 (sim3102phx)	卢 🕒 🚰	×		
- Worksheet 2	View Source	Source		
Sort Map		No worksheet I	has been selected.	Drag a worksheet from the
	Mappings			
		None	Sort	Included Column
۰ III • •				
Options				
·				
Carry Along Data For Like Sort Level	s			

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

Setup Results Verification		
Worksheet 1 (sim3102phx)	🛃 🖹 🔒	×
Worksheet 2	View Source	Source
PSort Map	Mappings	Select Object
		Project
4 •		Eta Stacked NonParEta NonParOvr NonParStak NonParStak Omega Omega Omega Stderr Overall Residuals Secondary SecondaryStderr StrCovr
Options		StrCovrCat
☑ Carry Along Data For Like Sort Leve	ls	Table01 Theta ThetaVariance VarCovar Select Cancel
		Select Cancel

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

Worksheet 1 (sim3102phx) <mark> Worksheet 2 (PK Model.Table</mark>	01 View Source Mappings	Mapped to result of: pkfix_pd.Workflow.PK Model.Table01						
		None	Sort	Included Column				
	Scenario	۲	0	0				
	repl	۲	0	0				
	ID	0	۲	0				
	time	۲	0	0				
	Ка	0	0	۲				
	V	0	0	۲				
	Ке	0	0	۲				
•	•			<u>.</u>				
Options								

- Execute the Merge Worksheets object.
 Right-click on the resulting worksheet and Send To> Data>Column Properties.

Setup R	esult	s Verificati	ion												
H 🖬 🛛		i 🦻 🖪													
Filter:					ID	TIME		CO	NC	EFF		OSE	Ka	v	Ke
🖄 Output 🛙	S Output Data			1	0	Ο.		•			100	0.795626	1.36971	0.177016	
🕮 Resi	11		2		1	0.25		10	.456213	29.632273	•		0.795626	1.36971	0.177016
🖹 TextOu		<u>S</u> end To		•	System		•	23	.803469	40.989257		1	0.795626	1.36971	0.177016
📑 Setti	Setti Refresh Results Copy to Data Folder Export Print		ults	•	Data		⊁	墨	Append	d Worksheets			0.795626	1.36971	0.177016
			a Folder	Folder AutoP Plottin		ot	► <u>80</u> ► 2		BQL				0.795626	1.36971	0.177016
						I			· ·				0.795626	1.36971	0.177016
					NCA and Toolbox		۲	ф.	Column	n Transformation			0.795626	1.36971	0.177016
		<u>P</u> KS		+	WNL5 Classic Modeling		۲	Crossproduct Worksheet		ts		0.795626	1.36971	0.177016	
		Dependenci	es		Phoenia	-		4	Filter W	/orksheet			0.795626	1.36971	0.177016
	_		10		IVIVC			B	Join Worksheets		100	0.795626	0.714979	0.0643591	
					Table		۲	瀲	Merge Worksheets			i		i	
Options					NONM	EM	۲		Pivot Worksheet						
Carry Alor	ng Da	ta For Like Sor	t Levels		SAS		۲	2	Rank W	/orksheet					
					SigmaP	lot	۲	Шř	Split Wo	orksheet					
					SPlus		۲		Stacker						
					R		۲								

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.)

ter:		ID	TIME	CONC	EFF	DOSE	Kaf	Vf	Kef
Output Data	1	1	0.	•		100	0.795626	1.36971	0.17701
🕮 Result	2	1	0.25	10.456213	29.632273	•	0.795626	1.36971	0.1770
Text Output	3	1	0.5	23.803469	40.989257	•	0.795626	1.36971	0.1770
📑 Settings	4	1	1	42.090574	49.779381	•	0.795626	1.36971	0.17701
	5	1	2	48.252579	55.837319	•	0.795626	1.36971	0.17701
	6	1	4	45.250264	44.868387	•	0.795626	1.36971	0.17701
	7	1	8	20.517478	53.234272		0.795626	1.36971	0.17701
	8	1	12	10.608362	32.247845	•	0.795626	1.36971	0.17701
	9	1	20	2.935427	15.502231	•	0.795626	1.36971	0.17701
	10	2	0.			100	0.795626	0.714979	0.064359
ptions Defaults	10	2		•	15.502231				
) => ID [Double]			Kef						

- 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.

Object Browser 🧭	pkfix_pd >> Workflow >> PD Mo	del Ind PK fixed	
E ⊑ III	Setup Results Verification		
	♥ Main (Column Properties) Model ♥ Dosing ♥ Parameters ♥ Parameters.Mapping	View Source Mappings ID TIME CONC EFF DOSE Kaf	Select Object Project Project OmegaStderr Overal Residuals Secondary Secondary Secondary StrCovr StrCovr StrCovrCat Theta Theta ThetaVariance VarCovar
	✓ Population? Structure Type: PK/Emax ▼ Parameterization: Absorption: Micro ▼ Extravascular tlag? Ka = Ke ? ✓ Closed form?	Mapping Ou Parameters Ir Num Compa 1 Elim. Cpt.	Merge Worksheets

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 ヂDosing ヂParameters		l.Data.sim3102pł	או				
Parameters.Mapping	Mappings						
	None		ort ID	Aa	Time	EObs	
	D C	(•	0	0	0	
	TIME O			0	۲	0	
	CONC	(0	0	0	
	EFF C	(0	0	\bigcirc	
	DOSE C	(۲	0	0	
	Mapping Output Sort Ord	ler					
Population? Structure	Parameters Input Options	Initial Estim	ates Run Options	Model Text Plo	its no warnings	3	
Type: PK/Emax			(Set WNL		Edit as Grap	phical >> Edit as Textual >>
Parameterization: Absorption:	Num Compartments:	Parameters:	Statements:				
Micro 💌 Extravascular	🕶 1 🔤 💌	Ka	cfMicro(A1, Ke, first = (A	\a = Ka))			
🗌 tlag? 📃 Ka = Ke ?	Elim. Cpt.?	V	dosepoint(Aa)				
Closed form?		Ke	C = A1 / V				
Infusions possible?	Freeze PK?	EC50	E = E0 + Emax * C / (E0	C50 + C)			
Effect		EO	error(EEps = 1)				
Emax: 🗹 Baseline 🗖 In	hibitory 🔲 Sigmoid	Emax	observe(EObs = E + EE	ps)			
🗌 Fractional 🔲 F	reeze						
Residual Error:							
E EObs EEps = Additive	BQL?						
Stdev: 1 8.422	49 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	Parame	eters Input O	ptions In	itial Estima	ites Run	Options	Model Text	Plots no warnings	
Structural	Covar. Type Fixe	d Effects	Random Eff	iects Sec	ondary	Scenarios				
SPam	Style	Fixef	Ran Ranef	Code						
Ка	Product*exp(et]tvKa		Ka = tvł	Ka * Kaf [*]	dKadKaf				
V	Product*exp(et	tvV	\checkmark	V = tvV	* Vf^dVd	IVf				
Ке	Product*exp(et	tvKe	\checkmark	Ke = tvl	Ke * Kef	dKedKef				
EC50	Product*exp(et	tvEC50	✓ nEC50	EC50 = 1	tvEC50 *	exp (nEC5	0)			
EO	E0 Product*exp(et		✓ nE0	E0 = tvE0 * exp(nE0)						
Emax	Emax Product*exp(et		🗸 nEmax	ax Emax = tvEmax * exp(nEmax)						
Covaria	te Center	Pos?	Direction	Ka	V	Ke	EC50	E0		
× Kaf			Backward	Yes	No	No	No	No		
x Vf			Backward	No	Yes	No	No	No		
× Kef			Backward	No	No	Yes	No	No		
Add Co	ovariate		•				- F			
Add From	m 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		Structure	Parame		Input Options		Run Optic	
Structural	Covar. T	ype Fix	ed Effects	Rar	ndom Effects	Secondary	/ Scen	arios
Fixef	Initial	Lower*	Upper *	Freeze	Estimate		Units *	(*=optiona
tvKa	1				1	Accept		
tvV	1				1	Accept		
tvKe	1				1	Accept		
tvEC50	35				40.7002	Accept		
tvE0	10				10.0743	Accept		
tvEmax	100				99.6171	Accept		
dKadKaf	1			V	1	Accept		
dVdVf	1			V	1	Accept		
dKedKef	1			V	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>Strucutral 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.