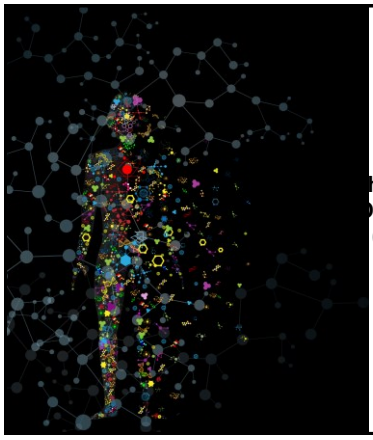


hool:
ne compartment
0-order input

PK3: Protocol

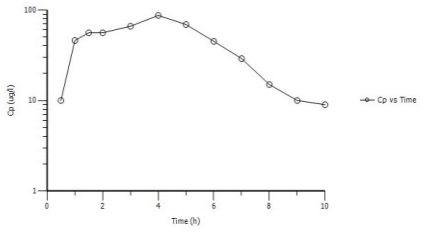
- 1 subject received a 20mg (20,000 µg) oral dose of a highly polar drug
- Plasma concentration samples were collected
- From previous IV bolus studies, the drug is known to have a 1 compartment elimination

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

CERTARA

PK3: Exploratory Data Analysis

- Plasma Concentrations vs Time



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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PK3: Objective

- Apply a 1-compartment model in terms of CL and V/F
- Generally absorption is thought of as a 1st-order process, although in some cases it is better described by 0-order input, which resembles constant rate infusion
- Fit and discriminate between 1st- and 0-order models
- Find estimates for:
  - Ka = 1st order absorption via GI tract
  - Tlag = lag time to reach the GI absorption site

  } Built-in model uses Ka, Tlag
  - Tabs = input time for the zero order model

  } PML text model parameter
  - V/F = volume of distribution
  - CL = clearance

  } Distribution and clearance parameters are the same in both models

Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

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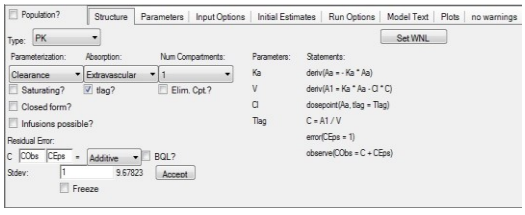
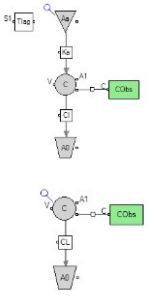
PK3: Built-in 1-compartment PK model with Tlag



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

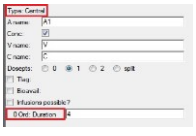
CERTARA

PK3: Graphical Model with 1st vs 0-order input to Central



1st-order with Tlag:

0-order with duration:



Gabrielsson & Weiner, Pharmacokinetic and Pharmacodynamic Data Analysis - Concepts and Applications, 5th Edition, Swedish Pharmacology Press (2015)

CERTARA

PK3: Textual Model: PML Code

```
test(){
    # differential equation to describe the PK
    deriv(A1 = - CL * C)
    # Zero order input to the central compartment
    dosepoint(A1, duration = Tabs)
    # initial concentration of the central compartment
    C = A1 / V
    # observed concentrations and error model
    error(CEps = 1)
    observe(CObs = C + CEps)
    # structural parameters from the built-in model
    stparm(V = tvV)
    stparm(CL = tvCL)
    # initial parameter estimates, including Tabs
    fixef(tvV = c(, 100, ))
    fixef(tvCL = c(, 45, ))
    fixef(Tabs = c(, 4, ))
}
```

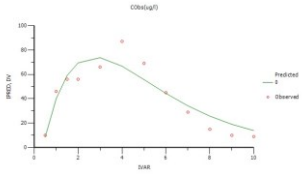

PK3: Initial Estimates

- CL = 45 L/hr, obtained from NCA terminal phase regression
- V = 100 L/kg, obtained from NCA analysis
- Ka = 1 1/hr – can be adjusted on Initial Estimates tab
- Tlag = 0.5 hr, time of the first observed concentration
- Tabs = 4 hr, determined from plot (Tmax)

Demo

PK3 Results: Built-in model with Ka and Tlag

- Fit

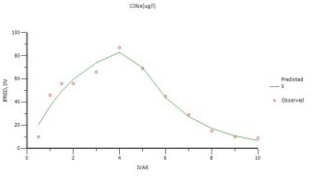


- PK Parameter Estimates

	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvKa	0.424468	1/h	0.14029612	33.052224	0.09271883	0.75621717	888550
2	tvV	99.3385	l	32.626676	32.843939	22.188304	176.4887	4.8667E+10
3	tvCl	42.1668	l/h	3.1523959	7.4760141	34.712533	49.621067	0.25694
4	tvTlag	0.394767	h	0.11303539	28.633445	0.1274795	0.6620545	0.00018185
5	stdev0	9.67823		1.9755506	20.412313	5.0067731	14.349687	

PK3 Results: PML model with 0-Order Duration (Tabs)

- Fit



- PK Parameter Estimates

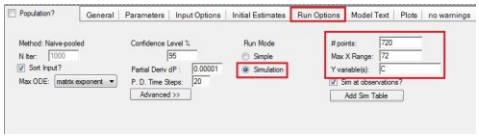
	Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvV	78.5031	l	12.942952	16.487186	48.656854	108.34935	3.9001
2	tvCL	46.5534	l/h	2.2441479	4.8205887	41.37843	51.72837	0.11124
3	Tabs	5.12241	h	0.32320272	6.3095832	4.3771095	5.8677105	0.002516
4	stdev0	6.68939		1.365467	20.412429	3.5406444	9.8381356	

PK3: Summary

- Derive initial estimates
- Fit 1-comp PK extravascular model with lag time
- Explore results
- Try a zero order input model
- Review results:
  - plot
  - residuals
  - overall diagnostic
  - parameter precision (theta)

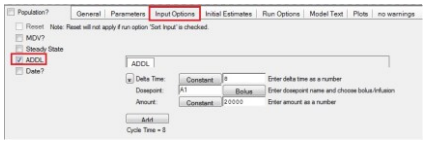
PK3: Simulate Multiple Doses: Run Options

- Run Options tab: set to Simulation mode. Specify number of points, output time range, and sim variable as shown:

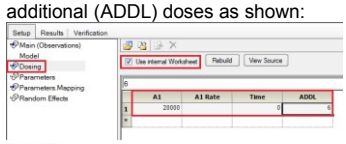


PK3: Simulate Multiple Doses: ADDL inputs

- Input Options tab: check the ADDL checkbox. Enter dosing cycle time information as shown:

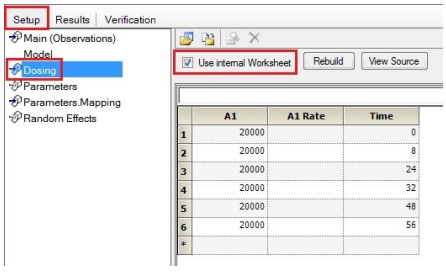


- Setup | Dosing: enter initial dose amount and the number of additional (ADDL) doses as shown:



PK3: Simulate Multiple Doses: Variable or Uneven dosing

- Setup | Dosing: fill out the spreadsheet with administered doses and times as shown:



	A1	A1 Rate	Time
1	20000		0
2	20000		8
3	20000		24
4	20000		32
5	20000		48
6	20000		56
*			

Questions?

Certara University

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  - Fundamentals of Pharmacokinetics and Pharmacodynamics
  - Noncompartmental data analysis
  - Programming Bootcamp
  - Partner Lectures and Webinar series
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PML School: Materials

- Each model will be made available in Certara Forum
  - Link to live webinar and presentation slides
    - https://support.certara.com/forums/forum/34-pml-school/
  - Model text as file download
    - Can be imported into Phoenix model object to be run on a new dataset
  - Questions and comments can be exchanged in the Forum
    - Topic 4: Multiple Absorption Routes using the Phoenix Graphical Model