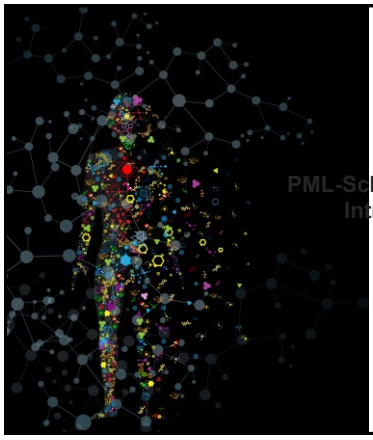

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PML-School: Introduction (brief)

PML School – who is it?

About Our Speakers

Dr. Bernd Wendt has been teaching as a trainer at Certara and is a lecturer at the Ludwig-Maximilians-Universität (Munich) for more than 5 years, providing seminars in pharmacokinetics and molecular modeling. He is currently heading the global support group at Certara.

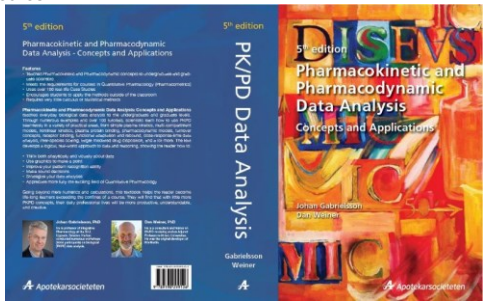
Christopher Mehl is the Customer Support Manager, and is a software trainer at Certara since 2003. He has conducted over 200 training courses with Pharsight desktop products such as Phoenix WinNonlin, IVIVC, NLME, PKS, and Trial Simulator. These include workshops at the US Food and Drug Administration, universities, customer sites, and courses open to the public.

Dr. Daniel Weiner is the co-author of Pharmacokinetic and Pharmacodynamic Data Analysis: Concepts and Applications, now in its 5th ed. Dr. Weiner is an Adjunct Associate Professor with Division of Pharmacotherapy and Experimental Therapeutics in the School of Pharmacy, University of North Carolina and is an Affiliate Professor of Pharmacometrics, Center for Translational Medicine in the School of Pharmacy at the University of Maryland. During his career he has provided PK/PD training to over 2,000 students.

CERTARA 2

PML School: Selection of Models

- Source:



CERTARA 3

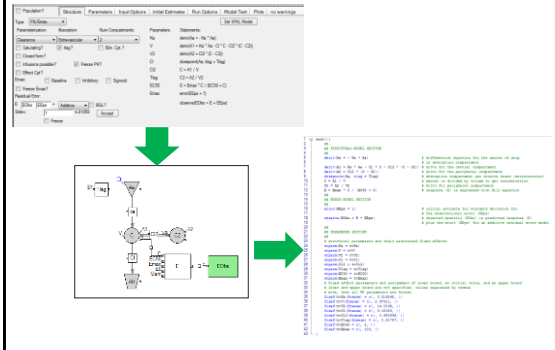
PML School: Selection of Models

PK Models	(PK)PD models

• 3-compartment model
• Multiple Dose
• Parent Metabolite Kinetics
• IVPO, simultaneous fit
• Michaelis-Menten
  ○ Dose Escalation
  ○ Multiple Dose
• Target-Mediated Drug Disposition (TMDD)
• Zero Order Absorption
• Allometric Scaling
• Enterohepatic recirculation
	• PKPD Link
	• Hill model, Logistic model
	• Tumor Growth Inhibition
	• Enzyme Inhibition
	• PKPD Link, Initial Estimates
	• Warfarin
	• Indirect Response, Dose Escalation
	• Multiple Dose, Indirect Response
	• Dose Response, Dose Escalation, ED50
	• Transduction, Transit Compartments

CERTARA 4

PML School: From graphical to textual model

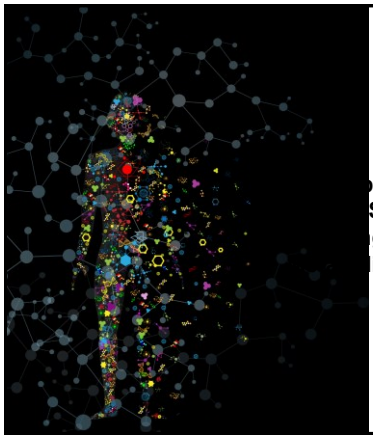


CERTARA 5

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
    - Or can be entered into the Certara Support portal at:
      - https://support.certara.com/support
    - Or can be sent as emails to support@certara.com

CERTARA 6



rary:
Simultaneous
g of Parent and
ite Kinetics

PK19: Objective

- Simultaneously fit drug and metabolite data
- Model capacity-limited elimination (Michaelis-Menten kinetics)
- Find estimates for:
  - Vc – volume of the central compartment for parent
  - Vt – volume of peripheral tissue compartment for parent
  - Cld – inter-compartmental distribution rate for parent
  - Km – Michaelis-Menten constant
  - Vmax – maximum metabolic rate
  - Kme – 1st-order constant for elimination of metabolite
  - Vme – volume of distribution for metabolite

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

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PK19: Protocol

- 1 subject received IV infusion doses of drug A at levels of 10, 50, and 300 umol/kg on separate occasions
- After each dose administration, concentrations of drug A and metabolite M were measured in the blood plasma
- Plasma samples were collected

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

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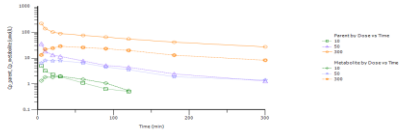
PK19: Exploratory Data Analysis

- Semilog plot of parent and metabolite concentrations by dose versus time



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

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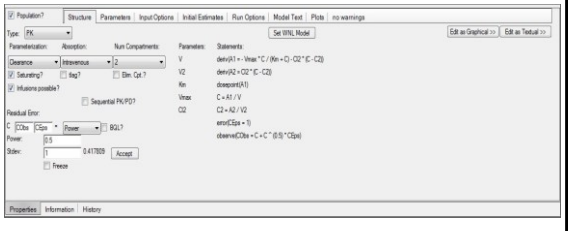
PK19: Built-in Model for Parent compound



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

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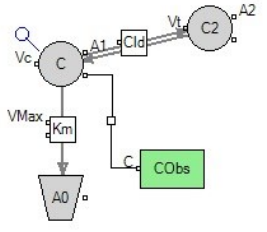
PK19: Graphical Model for Parent compound



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

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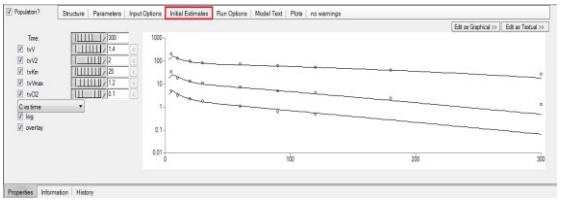
PK19: Initial Estimates for Parent Compound

- Vc = 1 L/kg, obtained from Dose / C(0)
- Vt = 1 L/kg, obtained from previous studies
- Cld = 0.1 L/min, obtained from previous studies
- Km = 15 umol/L, from NCA (Clavg = Vmax/(Km + Cpavg))
- Vmax = 1.4 umol*min/kg, from NCA

PK19: Initial Estimates tab for Parent compound

- This is a handy tool that allows you to visualize the predicted concentrations from given parameter estimates, overlayed with the observed concentrations:



PK19: Simultaneous Fit of Parent and Metabolite

- Once you are satisfied with the model fit for the Parent compound only, make a copy of the model and paste it back into the workflow. This will retain all of the model settings, structural parameters, and parameter estimates from the previous run.
- Edit the model in Textual mode to add the Metabolite observations and structural parameters to the model.

PK19: Textual Model: PML Code

```
test(){
    #differential equations for parent, central and peripheral compartments
    deriv(A1 = - (VMax * C / (C + Km))- (Cld * (C - C2)))
    deriv(A2 = (Cld * (C - C2)))
    #differential equation for metabolite
    deriv(A0 = (VMax * C / (C + Km))- (A0 * Kme))
    #Central compartment dose and concentration
    C = A1 / Vc
    dosepoint(A1, duration = (5))
    #Peripheral compartment concentration
    C2 = A2 / Vt
    #Parent observation and error term
    error(CEps = 1)
    observe(CObsPA = C + C^0.5 * CEps)
    #Metabolite concentration and observations
    Cme = A0 / Vme
    observe(CObsME = Cme + Cme^0.5 * CEps)
    #PK parameters (fixed effects) with initial estimates
    fixef(Vc = c(0, 1, 5))
    fixef(VMax = c(0, 1.4, 5))
    fixef(Km = c(0, 15, 100))
    fixef(Vt = c(0, 1, 10))
    fixef(Cld = c(0, 0.1, 5))
    fixef(Kme = c(0, 0.15, 2))
    fixef(Vme = c(0, 0.3, 5))
}
```

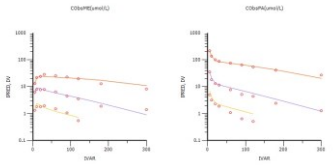

PK19: Initial Estimates for Simultaneous Fit

- Vc = 1.4 L/kg
- Vt = 2 L/kg
- Cld = 0.1 L/min → From modeling the parent data
- Vmax = 1.2 umol*min/kg
- Km = 25 umol/L
- Kme = 0.15/min, obtained from previous studies
- Vme = 0.3 L/kg, obtained from previous studies

Demo

PK19: Results

- Fit



- PK Parameter Estimates

Parameter	Estimate	Units	Stderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
Vc	1.06406		0.027359459	2.5712327	1.008846	1.119274	0.015125
VMax	1.64429		0.1985573	12.075564	1.2435827	2.0449973	0.093482
Km	54.7926	umol/L	15.598385	28.303278	23.496221	86.090979	285.17
Vt	2.00748		0.065565235	3.2660467	1.8751632	2.1397968	0.039571
Cld	0.128792		0.0095979685	7.4523018	0.1094224	0.1481616	0.00072293
Kme	0.14516	1/min	0.0060315835	4.1551278	0.1329877	0.1573323	0.0015699
Vme	0.290809		0.0084374167	2.9013602	0.2737815	0.3078365	0.0058568
stdev0	0.464128		0.054062001	11.64808	0.3550258	0.5732302	

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

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PK19: Summary

- Simultaneous fit of Parent and Metabolite data
- Build model for the Parent
- Derive initial estimates
- Fit the model to the data
- Learn how to code the model in PML
- Extend the model to include the Metabolite

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Questions?

PML School: Schedule for 2016

2016 PML School Schedule

Metabolite Kinetics
Simultaneously model plasma data of a drug and metabolite following 5-minute infusion. Metabolite clearance follows Michaelis-Menten kinetics
October 20, 2016 | 10am EST
Presenter: Chris Mehl

Two-compartment Repeated Oral Dosing
Fit multiple dose kinetic and dynamic data sequentially
November 3, 2016 | 10am EST
Presenter: Bernd Wendt

Nonlinear Kinetics
Fit nonlinear clearance for a highly plasma-bound compound using Michaelis-Menten elimination for two subjects with different Km
November 17, 2016 | 10am EST
Presenter: Chris Mehl

Simultaneous Fitting of IV/PO Data
Fit IV data first then IV and PO data separately and simultaneously
December 1, 2016 | 10am EST
Presenter: Bernd Wendt

Target-mediated Drug Disposition
Model circulating plasma target with a TMDD model
December 15, 2016 | 10am EST
Presenter: Dan Weiner

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