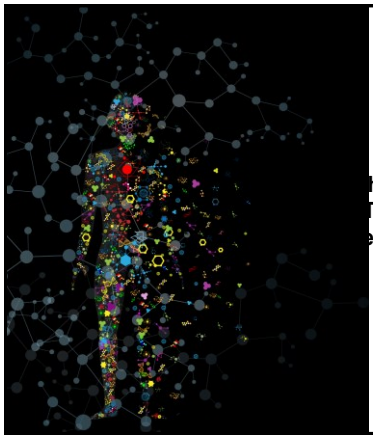

hool:
Two Compartment
ed Dosing

PK11: Objective

- Fit multiple dose PK data
- Freeze kinetics
- Fit a dynamic model to response-time data
- Find estimates for:
  - PK:
    - V_1 – volume of the central compartment
    - V_2– volume of peripheral tissue compartment
    - Cl – clearance from central compartment
    - Cl_2 – inter-compartmental distribution
    - K_a – absorption rate constant
    - T_{lag} – lag time between dosepoint and first measured concentration
  - PD:
    - EC_{50} – half maximal effective concentration
    - E_{max} – maximum drug-induced effect

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PK11: Protocol

- 1 subject received a single oral dose of 400 mg on Day 1
- On Day 5 same subject started to receive an oral dose of 400 mg *tid* (three-times-daily) for five days
- On Day 9 subject only received a single morning dose
- Plasma samples were collected at various times until 72h after the last dose

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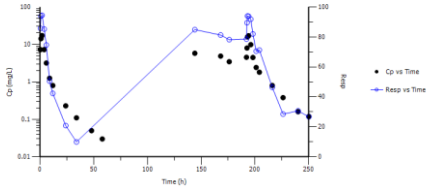
PK11: Exploratory Data Analysis

- Semilog plot of plasma concentrations and responses versus time



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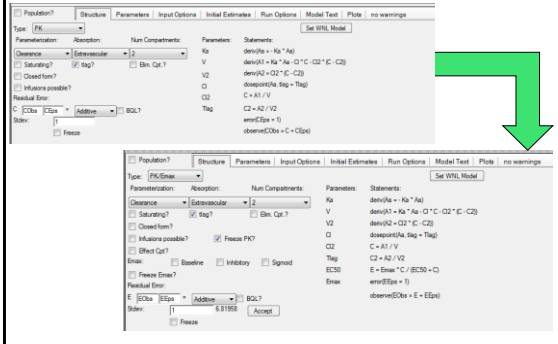
PK11: Built-in Model: From PK to PKPD



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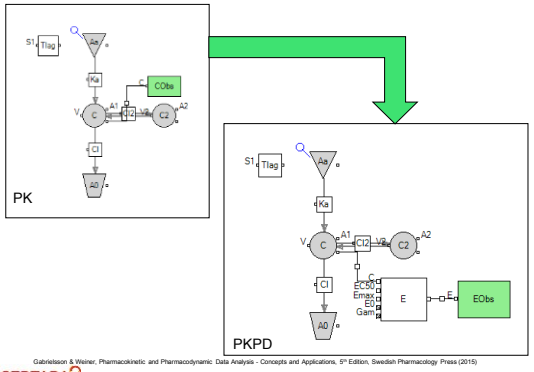
PK11: Graphical Model: From PK to PKPD



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PK6: Model equations

- Differential equations will calculate the change of amounts of drug in plasma for 1-compartment
  - $V \cdot \frac{dC}{dt} = \frac{dA1}{dt} = -Cl \cdot C$
- Ditto for 2-compartment
  - $V \cdot \frac{dC}{dt} = \frac{dA1}{dt} = -Cl \cdot C - Cl_d \cdot (C - C_t)$
- Adding extravascular input
  - $V \cdot \frac{dC}{dt} = \frac{dA1}{dt} = K_a \cdot Aa - Cl \cdot C - Cl_d \cdot (C - C_t)$
- Equation for Emax Model (Hill Equation)
  - $E = \frac{E_{max} \cdot C}{EC_{50} + C}$

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PK11: Textual Model: PML Code

```
test(){
  ##
  ## STRUCTURAL MODEL SECTION
  ##
  deriv(Aa = - Ka * Aa)                          # differential equation for the amount of drug
                                                 # in the absorption compartment
  deriv(A1 = Ka * Aa - Cl * C - Cl2 * (C - C2))  # differential equation for the amount of drug
  deriv(A2 = Cl2 * (C - C2))                     # in the central compartment
  dosepoint(Aa, tlag = Tlag)                     # absorption compartment (a dosing event 'extravascular')
  C = A1 / V                                     # amount is divided by volume to get concentration
  C2 = A2 / V2                                   # ditto for peripheral compartment
  E = Emax * C / (EC50 + C)                      # response (E) is expressed with Hill equation
  ##
  ## ERROR MODEL SECTION
  ##
  error(EEps = 1)                                # initial estimate for standard deviation for
                                                 # the observational error (EEps)
  observe(EObs = E + EEps)                       # observed quantity (EObs) is predicted response (E)
                                                 # plus the error (EEps) for an additive residual error model
  ##
  ## PARAMETER SECTION
  ##
  # structural parameters and their associated fixed effects
  stparm(Ka = tvKa)
  stparm(V = tvV)
  stparm(V2 = tvV2)
  stparm(Cl = tvCl)
  stparm(Cl2 = tvCl2)
  stparm(Tlag = tvTlag)
  stparm(EC50 = tvEC50)
  stparm(Emax = tvEmax)
  # fixed effect parameters and assignment of lower bound, an initial value, and an upper bound
  # lower and upper bound are not specified, values separated by commas
  # note, that all PK parameters are frozen
  fixef(tvKa(freeze) = c, 0.316365, )
  fixef(tvV(freeze) = c, 2.97511, )
  fixef(tvV2(freeze) = c, 14.0138, )
  fixef(tvCl(freeze) = c, 5.18185, )
  fixef(tvCl2(freeze) = c, 0.882968, )
  fixef(tvTlag(freeze) = c, 0.31797, )
  fixef(tvEC50 = c, 2, )
  fixef(tvEmax = c, 100, )
}
```

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PK11: Initial Estimates

- Cl = from NCA (CL_F_obs)
- Cl_2= Cl
- V_1 = Dose/Cmax
- V_2= from NCA (Vz_F_obs)
- K_a = start with 1
- t_{lag} = first measurable concentration after dose

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PK11: Modeling Strategy

- Run NCA for initial estimates
- Only Built-in options required to setup Phoenix Model
- Fitting pharmacokinetic data first
- Fixing pharmacokinetic parameters
- Fitting pharmacodynamic data

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Demo

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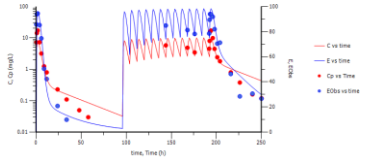
PK11: Results

- Fit



- PKPD Parameter Estimates

	Parameter	Estimate	Units	SEderr	CV%	2.5% CI	97.5% CI	Var. Inf. factor
1	tvKa	0.316365	1/h	0	0	0.316365	0.316365	0
2	tvV	2.97511		0	0	2.97511	2.97511	0
3	tvV2	14.0138		0	0	14.0138	14.0138	0
4	tvCl	5.18185		0	0	5.18185	5.18185	0
5	tvCl2	0.882968		0	0	0.882968	0.882968	0
6	tvTlag	0.31797	h	0	0	0.31797	0.31797	0
7	tvEC50	0.858452		0.14616848	17.015334	0.55468711	1.1622169	0.00037627
8	tvEmax	96.7161		3.1475387	3.2544103	90.170459	103.26174	0.18838
9	stdev0	6.01958		0.98431702	14.43369	4.7725884	8.8665716	

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PK11: Summary

- Simultaneous fit of IV and PO data
- Build model
- Derive initial estimates
- Fit the model to the data
- Learn how to code the model in PML

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