LAPP Leiden
Advanced PK-PD

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Hands on training
Non Clinical PKPD data exploration

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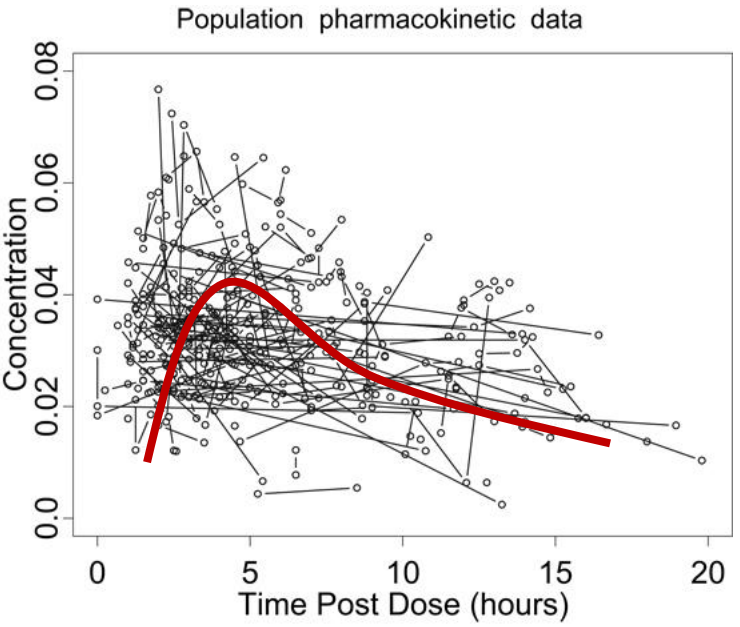
Concepts

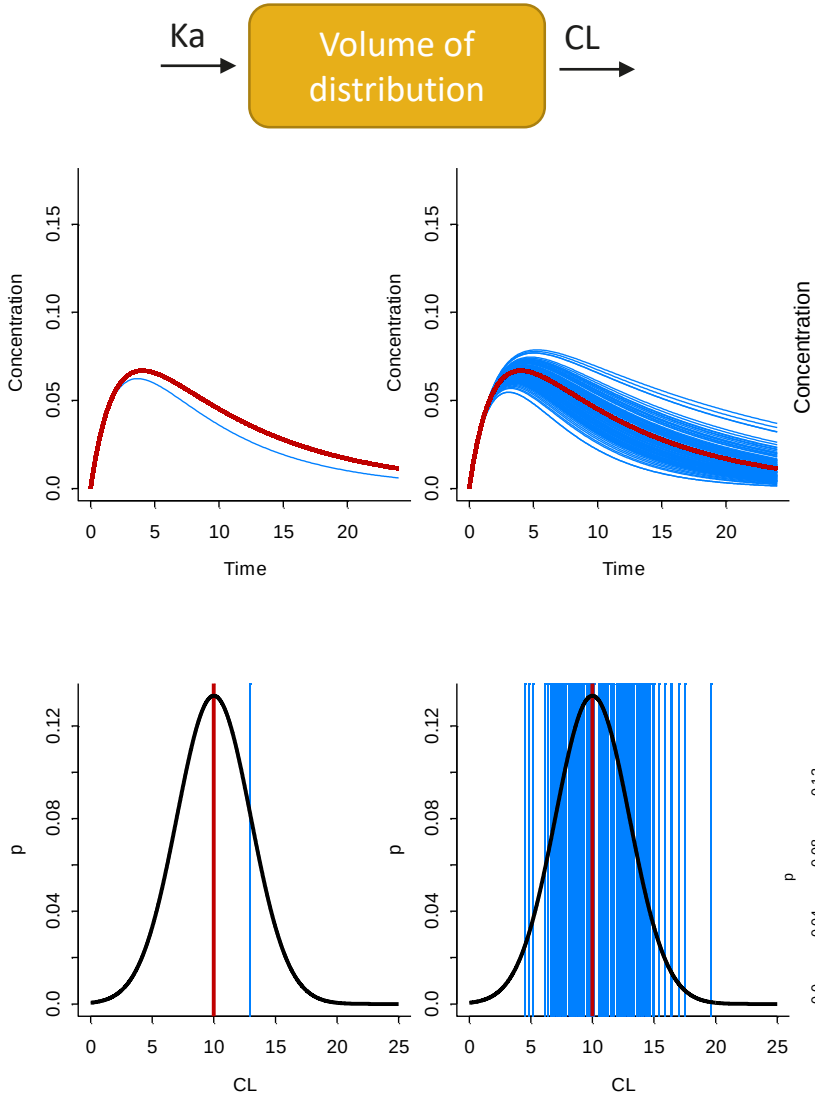
Population modelling: Illustrative example

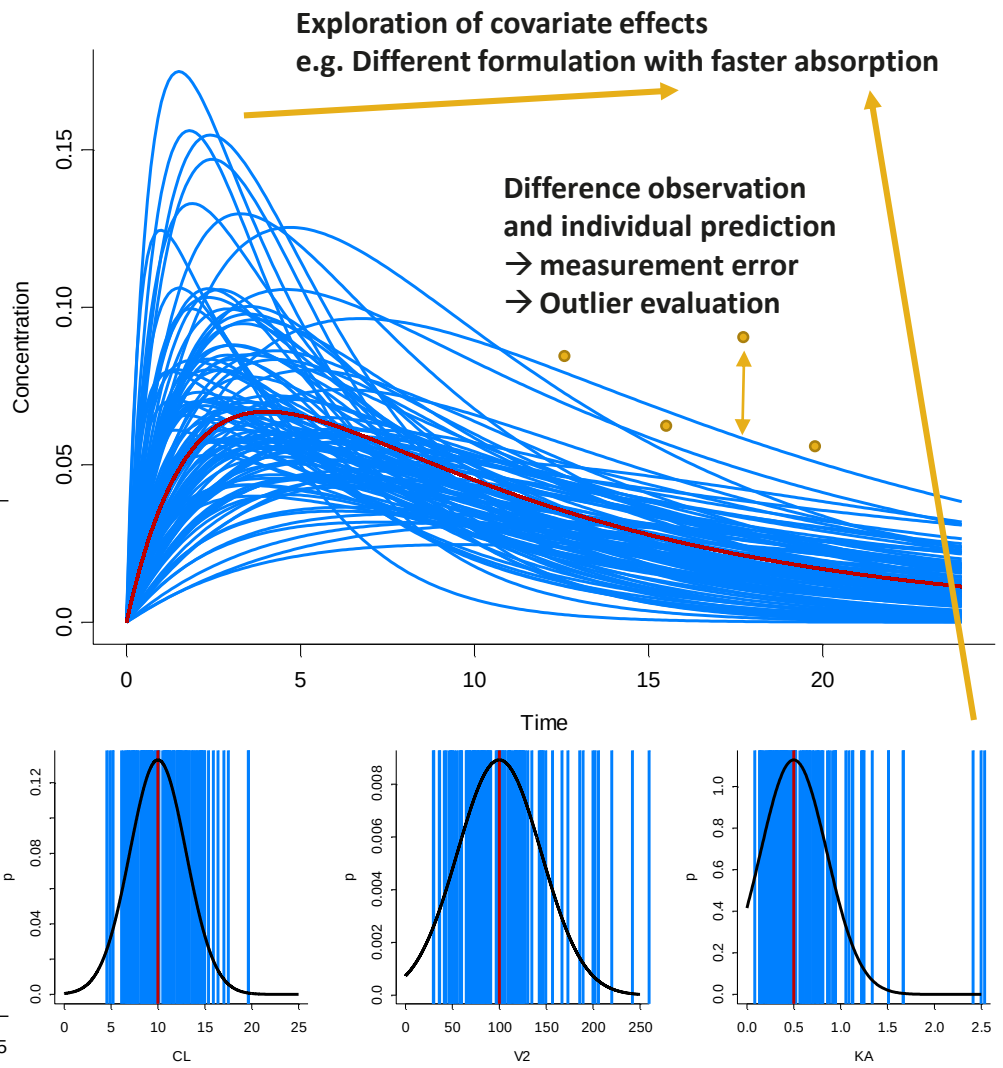
Quantification of inter individual variability and residual error

Fictive example :
Individual (line connections) PK profiles after single subcutaneous dose



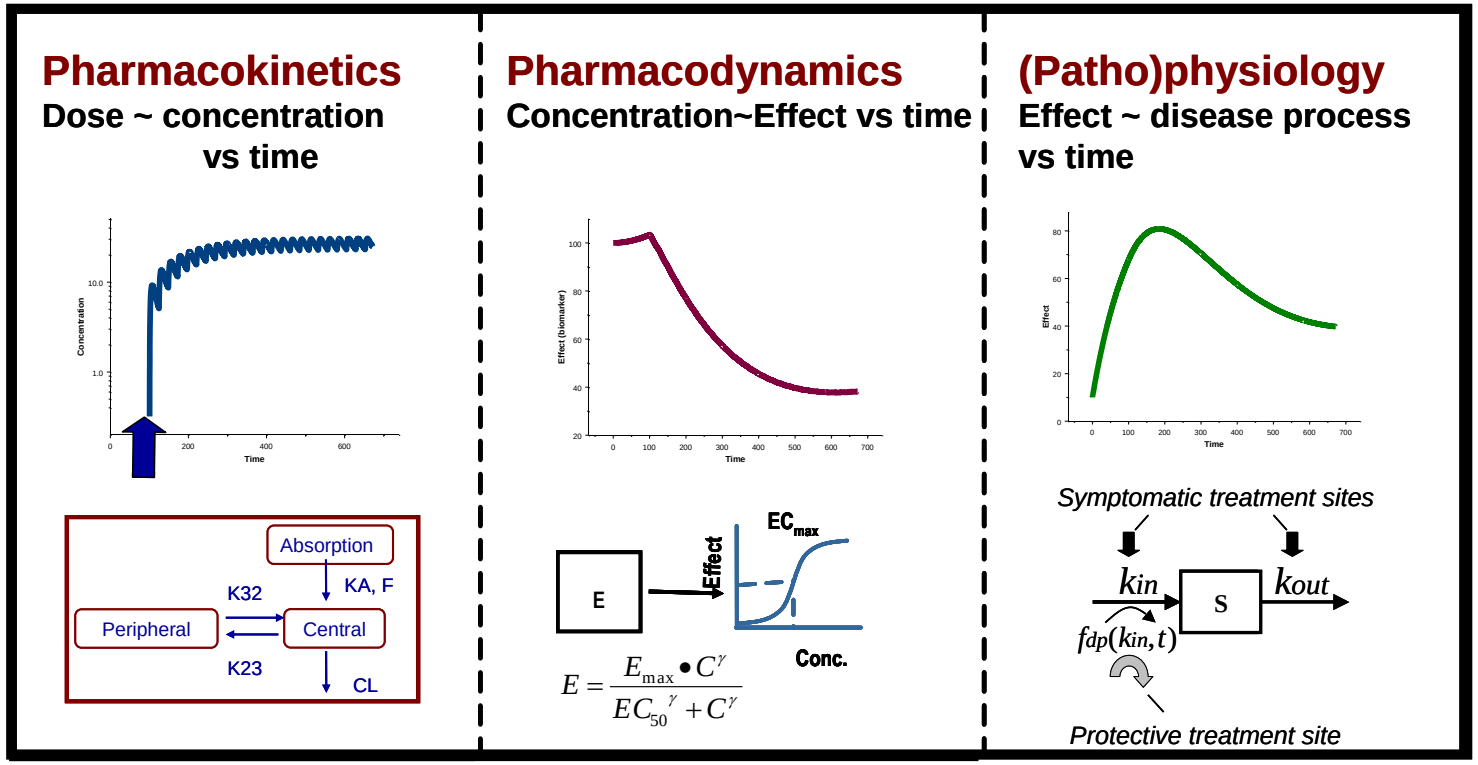
- Patients/Animals are different
- Assays are subjected to error





PK-PD-Effect integrated modeling

- Dose → Concentration → PD response → Clinical effect
  - Integrate pharmacokinetic, pharmacodynamic and physiological principles



Data integration

- Across **time points**
- Across **doses**
- Across **endpoints**
- Across **studies, populations and species**
  - Evaluate and quantify differences in patient populations (e.g. disease severity), species …
  - Analysis of sparse data is possible: Leverage information from rich (sub)studies
- Across **drugs**

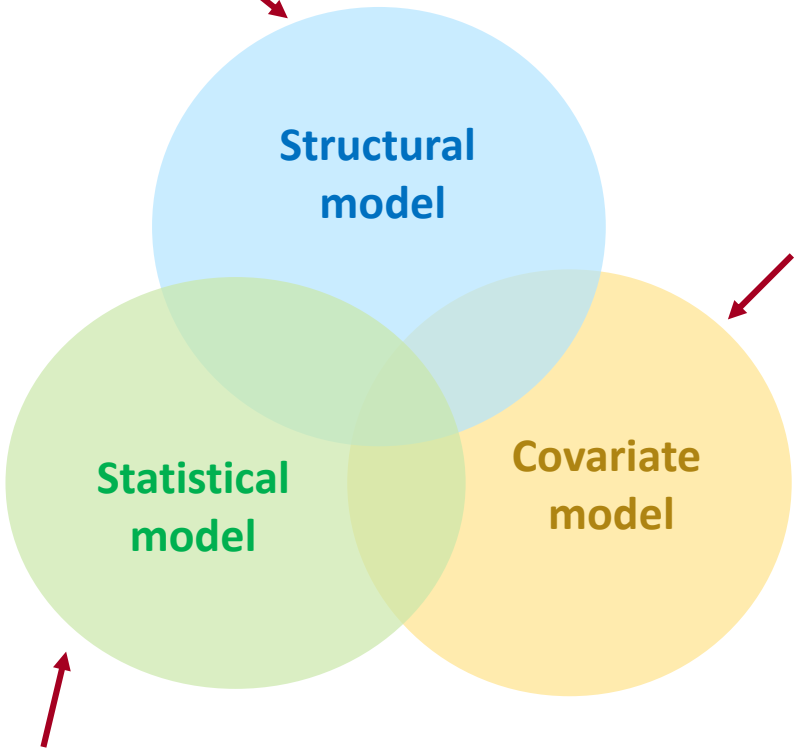
Sheiner (1992) *Learning and confirming in clinical drug development,* CPT

Population modeling as a tool to integrate and summarize PK-PD-Response knowledge

- Population model as tool to answer questions
  - Try to capture the most important processes
    - Keep it as simple as possible
    - But not too simple
  - Helps summarize all available knowledge
  - Responses are described in a quantitative fashion
  - Information from different sources can be integrated
  - Allows data driven hypothesis testing
  - Model simulations
    - predictions can be used to explore untested situations to support decision making

- Three main components of a population model

-PK: clearance (CL), volume of distribution (V) ...
-PD: production (Kin), degradation (Kdeg), drug effect ...

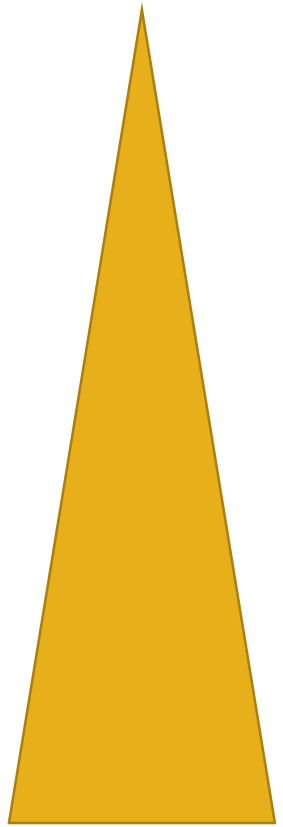


Explained inter individual variability:
-PK: CL, V increase with body weight
-PD: Kdeg decreases with body weight
-Compound specific effects to be investigated

-IIV: **Unexplained** inter individual variability
-Residual (measurement) error

Selection of model type depends on question, data and knowledge of the system

- Model types
  - Non-compartmental models
    - Basic description of observations using linear regression
  - Descriptive compartmental models
    - A series of interconnected compartments without any physiological interpretation
  - Semi-mechanistic compartmental models
    - A series of interconnected compartments with some physiological interpretation
  - Systems pharmacology - physiologically based PK models
    - PBPK: A series of interconnected compartments where each compartment represents a specific organ

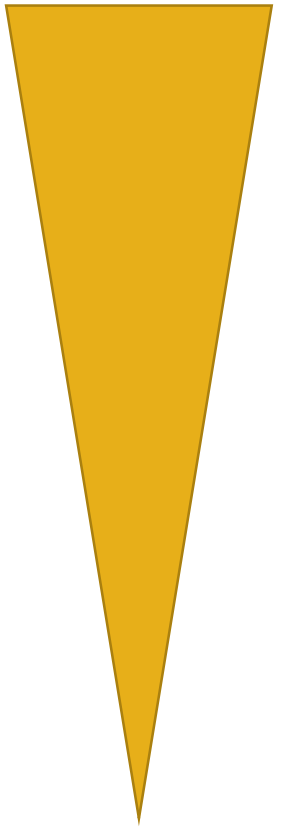


Purely descriptive - often limited value in predictions

Drug independent & systems based; High value predictions and extrapolation possible

<u>Align model type choice to</u>
-question
-available data
-system knowledge

→ Often feasible to develop/update along with drug development
→ Discuss assumptions and limitations
→ Predictions possible within boundaries



Straightforward reporting and interpretation

Time consuming (months to years)

Introduction to data exploration app

Practical information

- Link to shiny data exploration application
  - Account creation invitation via email address

- Live demonstration by Sven Hoefman: use of application
  - App developer (Richard Hooijmaijers) available online during course for help

- App remains accessible for certain period of time to allow participants to complete / re-visit exercises

Data exploration shiny app: essentials

- App designed for the present course: create explorative graphs for a dataset
  - All needed datasets are listed
- Getting started
  1. Select dataset: “sm_rat_pk_iv_sd.csv” (Optional: Click Table source data to get tabular overview)
  2. Select plotting panel (Default plotting)
     - Select following in Layer 1 → X value: “TIME”; Y value: “Cplasma”
     - Click create plots
       - Expand settings as desired → Create plots to re-generate plot
       - Re-set settings to starting point via “Clear fields”
  - Alternative: create plot via “show presets”
- Additional options
  - “Create plotly” instead of “create plots” → Interactive version of plot
  - Expert plotting: Allows more flexibility and plotting options → but less intuitive for users new to R programming
  - Save button to save plots
  - Complete refresh can be helpful: 

Explanation of dataset column names

- ID: animal number
- TIME: time (h)
- DOSE_MGKG: dose (mg/kg)
- CMPD: compound (SM, mAb)
- SPEC: species (Monkey, Rat, Mouse)
- BW: body weight (kg)
- ROUTE: route of administration (1: IV; 2: PO)
- NDOS: number of doses
- ADA: Animal anti drug antibody status (0: No; 1: Yes)
- C: Concentration (µg/mL), e.g. Cplasma, Cbrain
- BQL: Below quantification limit (0: No; 1: Yes)
- DV: Dependent variable
- BSL: Baseline (for efficacy and Safety biomarker)
- Percchange: Percent change from baseline (for efficacy and Safety biomarker)

- For the PKPD dataset, two differently structured datasets with same information is provided
  - Table “long” *versus* “wide”
    - Long: values of all variables in DV column; TYPE column specifies variable
      - TYPE: Cplasma, Cbrain, Efficacy_Biomarker, Safety_Biomarker
    - Wide: each variable as a separate column
      - Cplasma, Cbrain, Efficacy_Biomarker, Safety_Biomarker, Efficacy_Baseline, Safety_Baseline, Efficacy_Percchange, Safety_Percchange

Hands on introduction

Fictive non clinical drug development case – Compound properties

- Simplified compound properties + mechanisms of action
  - Selection between two lead compounds: small molecule and monoclonal antibody

Drug	SM	mAb
Format	Small molecule	Antibody
Administration	PO	SC
Target Selectivity	1A receptor 1B receptor	1A receptor
In vitro Potency (µg/mL)	1 µg/mL for 1A receptor	1 µg/mL for 1A receptor
Cross reactivity	Rodent & NHP	NHP, ±10x worse affinity for rodent
MW (g/mol)	1000	150000

1A receptor mainly expressed in brain, associated increased satiety (desired)
1B receptor mainly expressed in liver, associated with liver toxicity, relevance for potential clinical side effects unknown

Fictive study data availability

- Stepwise, simplified overview of drug development path
  - Dosage of 3, 10, 30 mg/kg; N=10 per arm; Set of time-points per study (sequential plasma sampling); Assay LLOQ 0.05 µg/mL

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 1a	SM	PK	IV Single dose	Rat	Data: sm_rat_pk_iv_sd.csv NCA: sm_rat_nca_iv_sd.csv
Step 1b	SM	PK	IV Single dose	Rat, Monkey, Mouse	Data: sm_trans_pk_iv_sd.csv NCA : sm_trans_nca_iv_sd.csv
Step 2	SM	PK	IV/PO Single dose	Rat	Data: sm_rat_pk_ivpo_sd.csv NCA: sm_rat_nca_ivpo_sd.csv
Step 3	mAb	PK	IV Single dose	Rat, Monkey	Data: mab_trans_pk_iv_sd.csv NCA: mab_trans_nca_iv_sd.csv
Step 4	SM + mAb	PKPD	PO/SC Q2D	Rat, Monkey	Data: trans_pkpd_q2d_long.csv; trans_pkpd_q2d_wide.csv

  - Step 1-4 can be performed using “default plotting”
    - For step 4: “expert plotting” option provides more flexibility

Purpose / goal(s) during each step

- Step 1
  - Toolbox practice: raw concentration profiles, NCA analysis results
  - Distinguish types of variability: inter- / intra-individual, inter-species
- Step 2
  - Compare effect of administration routes on PK
- Step 3
  - Inter-species PK variability for mAbs and its causes
- Step 4
  - Explore translational PKPD between compounds / doses / species
    - Plasma vs brain PK results
    - Safety and Efficacy biomarker results
    - Recommend safe/efficacious clinical dosing regimen per compound

Step 1: Assess variability between and within animals

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 1a	SM	PK	IV Single dose	Rat	Data: sm_rat_pk_iv_sd.csv NCA: sm_rat_nca_iv_sd.csv
Step 1b	SM	PK	IV Single dose	Rat, Monkey, Mouse	Data: sm_trans_pk_iv_sd.csv NCA : sm_trans_nca_iv_sd.csv

- Additional information
  - 1 week study; 3, 10, 30 mg/kg

- Step 1a
  - Explore PK profiles and NCA results
    - Discuss: variability – between (IIV) and within (measurement error) animals
    - Discuss: compare results between dose levels → E.g. Is the PK linear?

- Bonus - Step 1b
  - Explore NCA results: discuss species differences wrt allometric scaling

Step 2: Compare effect of administration routes on PK

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 2	SM	PK	IV/PO Single dose	Rat	Data: sm_rat_pk_ivpo_sd.csv NCA: sm_rat_nca_ivpo_sd.csv

- Additional information
  - 1 week study; 3, 10, 30 mg/kg
- Step 2
  - Explore and discuss: Compare PK profiles / NCA results between administration routes
- Bonus – Step 2
  - Discuss: impact of sampling schedule on NCA results

Step 3: inter-species PK variability for mAbs and its causes

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 3	mAb	PK	IV Single dose	Rat, Monkey	Data: mab_trans_pk_iv_sd.csv NCA: mab_trans_nca_iv_sd.csv

- Additional information
  - 2 week study; 3, 10, 30 mg/kg

- Step 3: Explore based on PK profiles / NCA results:
  - Discuss: Compare results between doses in monkey
  - Discuss: Compare results in terms of species differences between monkey and rat

- Bonus – Step 3
  - Generate hypotheses regarding differences between individual animals
    - Are there predictors of this variability in the dataset?

Step 4: Translational PKPD

	Drug	Study Type	Dosing	Species	Exploration datasets
Step 4	SM + MAB	PKPD	PO/SC Q2D	Rat, Monkey	Data: trans_pkpd_q2d_long.csv; trans_pkpd_q2d_wide.csv

- Additional information
  - 2w study; 3/10/30 mg/kg q2d dosing: Plasma PK + terminal brain PK sampling; PD: two biomarkers: efficacy and safety
  - 2 datasets contain same information but structured differently, depending on plot of interest dataset can be selected
    - Long: values of all variables in DV column; TYPE column specifies variable
    - Wide: each variable as a separate column
- Step 4
  - Explore Plasma vs brain PK results between compounds / doses / species
  - Explore Safety and Efficacy biomarker results between compounds / doses / species
- Bonus – Step 4
  - Explore expert plotting option→ In general tab: multiple panelling, subsetting and transformation options available
    - Underlying R code can be explored via: 
  - Discuss: impact of time point selection
  - Discuss: anticipated recommended safe/efficacious clinical dosing regimen per compound