POPULATION PK MODELING: THEORY, MODEL DEVELOPMENT AND APPLICATIONS

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OBJECTIVES

Following this workshop, the audience are expected to have a brief understanding of:

- ✓Why Population Pharmacokinetics (Pop PK) modeling are useful
- ✓When we develop Pop PK models
- ✓Basic theory of Pop PK models
- ✓Software and model development process
- ✓Case study of application

POPULATION PK ANALYSIS ARE EXPECTED IN NDA AND BLA

FDA U.S. FOOD & DRUG ADMINISTRATION

Population Pharmacokinetics
Guidance for Industry

DRAFT GUIDANCE

" Population PK analysis is frequently used to guide drug development and inform recommendations on therapeutic individualization (e.g., through tailored dosing) (Marshall et al. 2015; Lee et al. 2011; Bhattaram et al. 2005). Adequate population PK data collection and analyses submitted in marketing applications have in some cases alleviated the need for postmarketing requirements (PMRs) or postmarketing commitments (PMCs). "

European Medicines Agency

GUIDELINE ON REPORTING THE RESULTS OF POPULATION PHARMACOKINETIC ANALYSES

" The efficacy and safety of a new chemical entity (NCE) is generally characterised in phase III studies in a well defined restricted patient population. The pharmacokinetic (PK) information is used to extrapolate the safety and efficacy findings to the wider patient population who may receive the NCE in question. Today, population PK analyses are a regular part of the documentation of an NCE and form one way in which an applicant can choose to provide PK information.

Population PK studies are also submitted to regulatory agencies as part of type II variations of approved products or line extensions (e.g. in dose-finding studies in paediatric populations, for new indications or new formulations), and can in these applications constitute a large or even the main part of the clinical documentation. "

ABUNDANT EXAMPLES OF APPLICATIONS OF POP PK IN DRUG DEVELOPMENT OR POST-APPROVAL

Personalize and track your ADVATE® treatment[2,18]

myPKFiT™ for ADVATE is the first and only FDA-approved PK dosing software in the US for patients 16 and older with hemophilia A.[1]

For eligible patients on ADVATE prophylaxis, your healthcare provider may use myPKFiT software to analyze your personalized pharmacokinetic (PK) profile.

my PK FiT

With this information, your healthcare provider can tailor a dosing schedule that's right for you.

Free Download

The myPKFiT app is available in the App Store or on Google Play for iOS 10 and 11 and Android 6 and 7.

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https://www.advate.com/mypkfit

Plan your lifestyle and activities based on estimated FVIII levels

Use the FACTOR METER to check current and future estimated FVIII levels, which may help you make timely activity and lifestyle decisions based on relevant FVIII coverage.

Journal of Pain Research

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Population pharmacokinetic modeling to facilitate dose selection of tapentadol in the pediatric population

This article was published in the following Dove Press journal:
Journal of Pain Research

Estelle Watson[1]
Akash Khandelwal[1]
Jan Freijer[1]
John van den Anker[2,3]
Claudia Lefeber[1]
Mariëlle Eerdekens[1]

Objective: The main aim of this analysis was to characterize the pharmacokinetics (PK) of the strong analgesic tapentadol in 2-year-old to <18-year-old patients with acute pain and to inform the optimal dosing strategy for a confirmatory efficacy trial in this patient population.
Methods: The analysis dataset included tapentadol concentrations obtained from 92 pediatric patients receiving a single tapentadol oral solution (OS) dose of 1.0 mg/kg bodyweight in two single-dose PK clinical trials. Population PK analysis was performed using nonlinear mixed effects modeling. Simulations were performed to identify tapentadol OS doses in

WHY DO WE NEED POP PK MODELS

- Explain
  - Characterize the effect of various intrinsic and extrinsic factors on PK
    - demographics (age, sex, race)
    - disease (e.g. hepatic disorder, renal disorder, circulatory disorders)
    - genotype
    - administration related factors: route (e.g. oral, sub-cutaneous, intra-muscular, intra-venous, intra-thecal, inhaled, topical, suppository), site (e.g. arm vs. abdomen), volume and rate
    - meal, formulation, drug-drug interaction etc
  - Input for PK/PD models
- Predict
  - untested dosing regimens
  - untested populations
- Ultimate goal: optimize/control variability in exposure therefore response

POP PK MODELS IN PHASE I

- Prior to first-in-human: some prediction based on animal data to guide starting dose and sampling schedule
- Phase I studies (in both healthy volunteers and patients) and other dedicated clin pharm studies:
  - opportunity to collect intensive PK profiles
  - thorough characterization of structure model
  - initial assessment of within- and between-subject variation
  - definitive assessment for meal effect, formulation effect, organ dysfunction effect
  - preliminary assessment of covariate effect like demographics, population (healthy volunteer vs. patients) due to narrow range
- Utility of Pop PK models in Phase I
  - predict exposures at different dose level or frequency to guide dose escalation decision
  - input for PK/PD model for biomarkers, efficacy or safety endpoints to guide dose escalation decision

POP PK MODELS IN PHASE II

- Phase II studies in patients:
  - desirable to collect rich samples for better understanding of PK/PD relationship as this is a key goal for development at this stage
  - however the feasibility of collecting rich samples is limited by practicality: population, cost, patient-burden, typically not as intensive as phase I, some may be sparse
  - covariate effect assessment becomes more feasible and could guide phase III study design
- Utility of Pop PK models in phase II
  - it's all about Phase III study design: inclusion/exclusion criteria, dose regimens, meal instructions, contra-indicated medications
  - aid pharmaceutical science colleagues on dose strength and formulation development

POP PK MODELS IN PHASE III

- Phase III studies in patients:
  - typically only sparse samples allowed (e.g. near Cmax or pre-dose trough) when patients visit clinical sites, again due to patient-burden and cost
  - occasionally sub-study with intensive PK profiles (if inadequate assessment in this population in prior studies)
  - opportunity to apply sampling scheme optimization
  - much broader range for covariates therefore better assessment of covariate effect
  - significantly increased between-subject variation due to broader population, patient compliance issue, data reporting quality, deviation from protocol specified procedures etc
- Utility of Pop PK models phase III
  - thorough assessment of PK/PD relationship
  - justify dosing regimen recommendation in label

POP PK MODELS POST APPROVAL

- Phase IV studies in patients:
  - expansion of indication, population, route-of-administration or formulation
  - similar situation as Phase III
- Utility of Pop PK models in this stage
  - thorough assessment of PK/PD relationship
  - justify dosing regimen recommendation in label

Basic Theory of Pop PK Models

DRUG X – A CASE STUDY

A small molecule

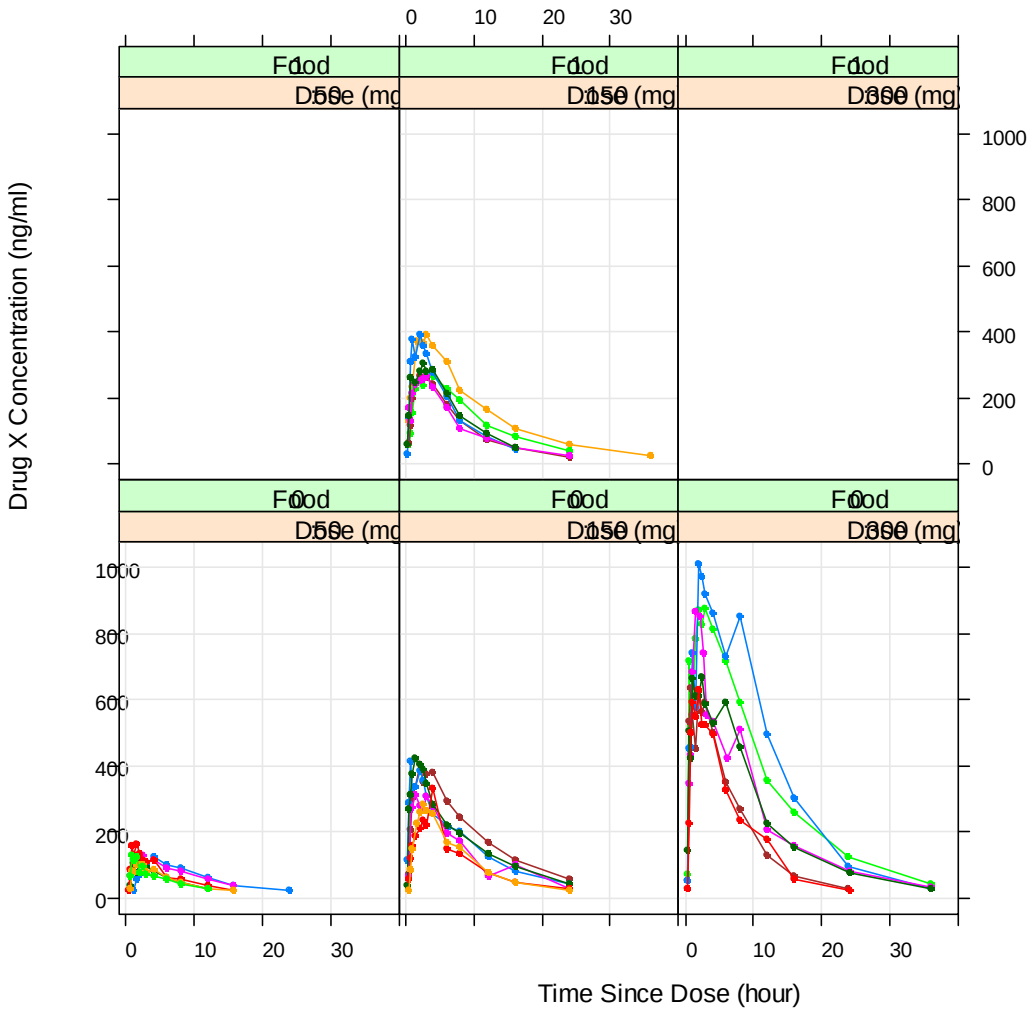
Oral administration

First-in-human study: 50, 150 and 300 mg

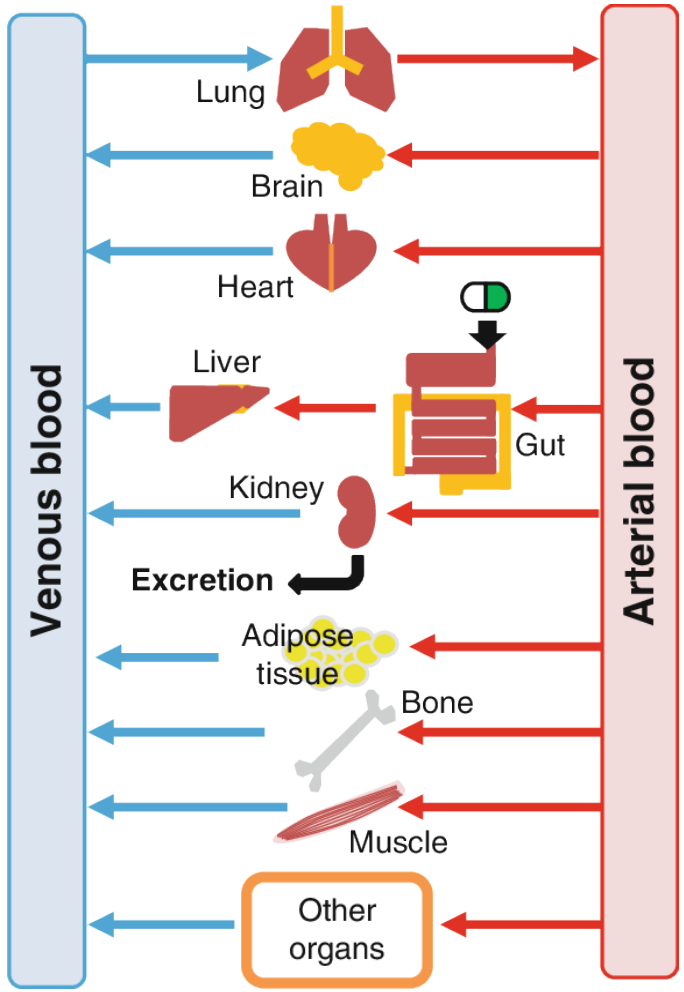
Conditions: fasted and fed

Sampling schedule: pre-dose, 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 and 36 post dose

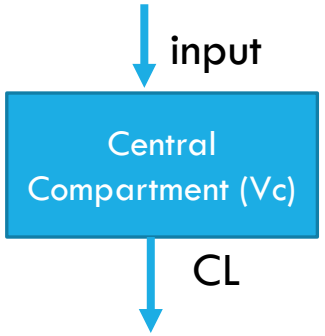
Overall impression: similar shapes of PK profiles across subjects, variability mainly around Cmax and Tmax with same dose level



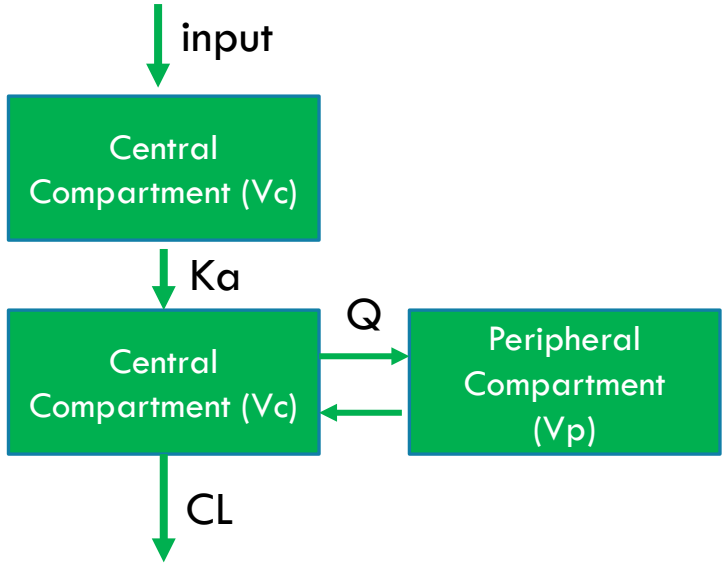
PHYSIOLOGICALLY BASED PK VS. POP PK (COMPARTMENT MODELING)



Compartment: a region of the body in which the drug is well mixed and kinetically homogenous



One compartment model



Two compartment model

MODELING STEPS

- ❑ Identify purpose of modeling
- ❑ Data gathering and data set construction
- ❑ Data exploration
- ❑ Define the structure model (closed form or differential equation)
- ❑ Define the stochastic model for random effects and residual errors
- ❑ Parameter estimation methods
- ❑ Develop covariate model
- ❑ Model evaluation

DATA GATHERING AND DATA SET CONSTRUCTION

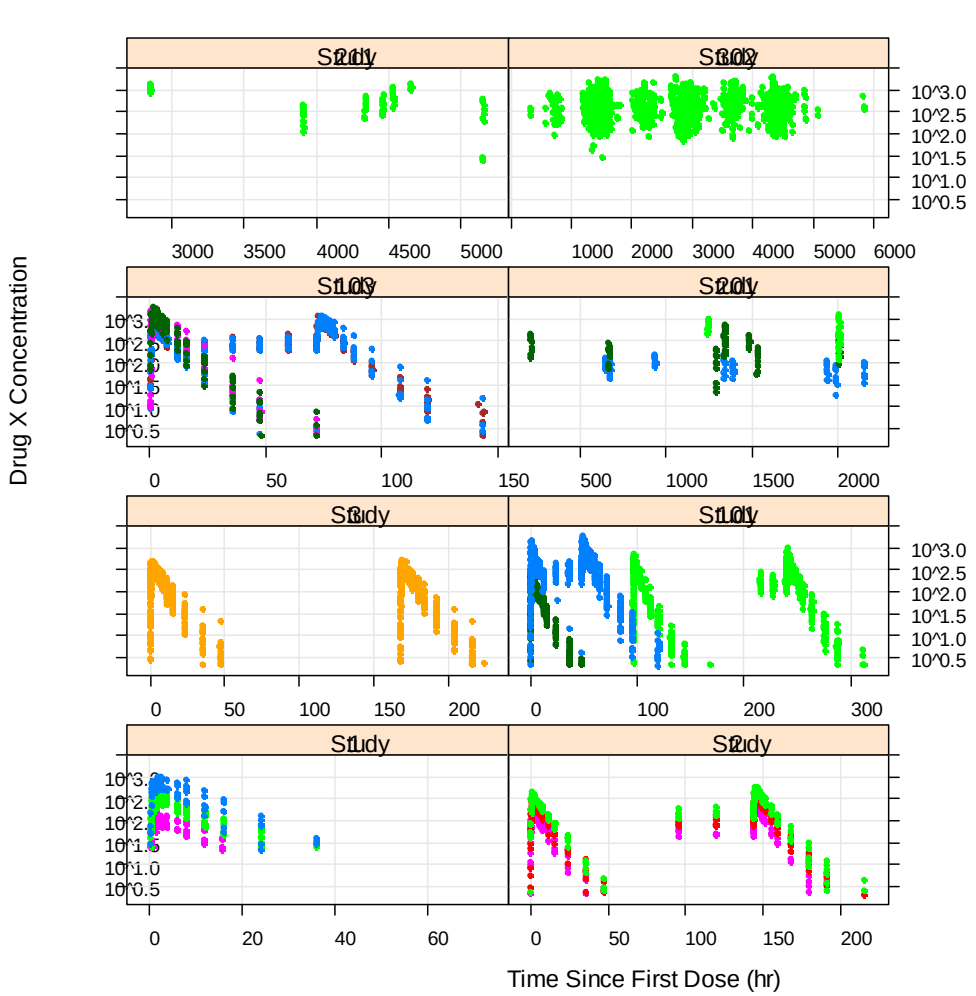
- Design the experiment (number of subjects, number of samples and timing of sample collection)
  - how much information does the data contain for the parameter of interest?
- collect dosing history (amount, rate and time), sample collection, concentration values
  - data error leads to problem in parameter estimation and inflated inter-subject variability and residual error
- Collect other important covariate information
  - take into consideration during design stage – do I have sufficient range for definite conclusion?
- Create a data set conforming to specific format requirement of a software (e.g. NONMEM, Monolix, Phoenix NLME)
  - pay special attention to syntax, otherwise a tiny error will make you frustrated!

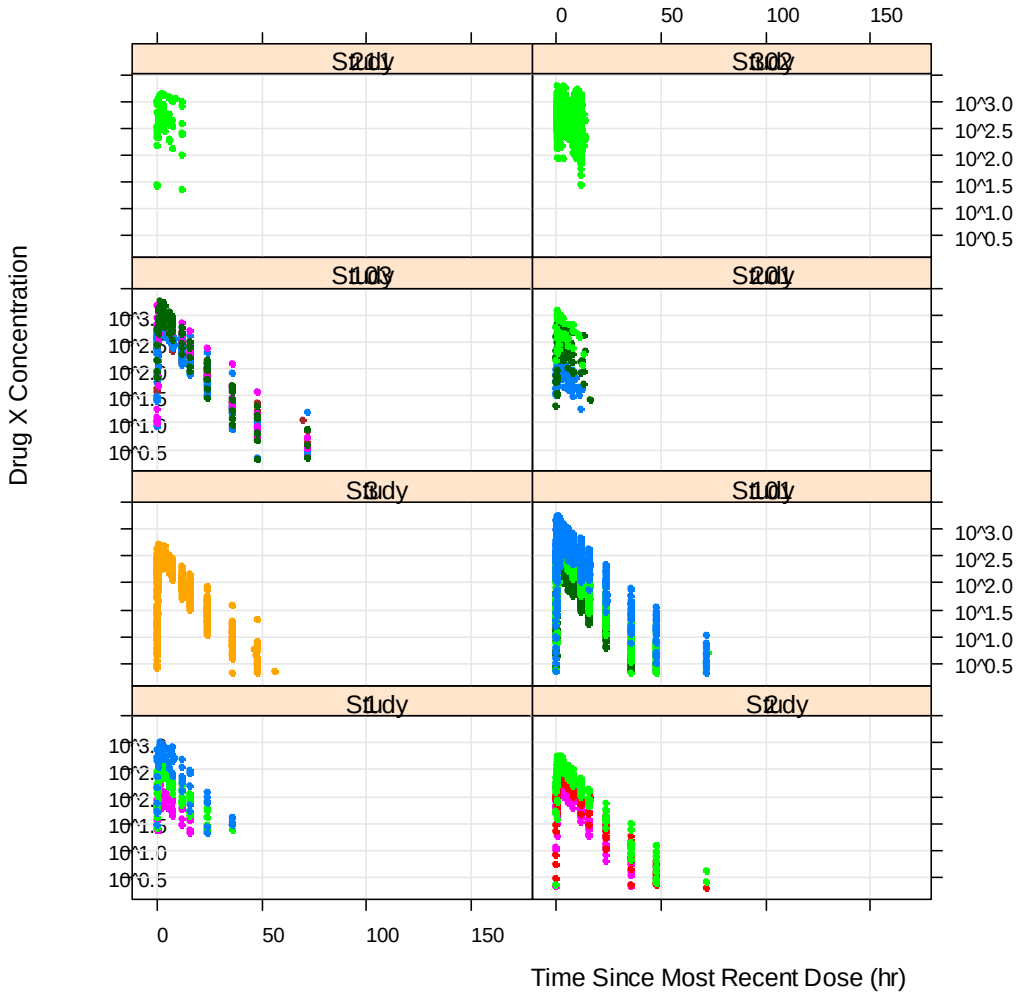
AN EXAMPLE OF NONMEM DATA SET

ID	TIME	AMT	EVID	DV	CMT	MDV
1	0	100	1	0	1	1
1	2.0931	0	0	4.3452	2	0
1	4.0262	0	0	.	2	1
1	5.868	0	0	2.5479	2	0
1	8.2031	0	0	2.311	2	0
1	12.197	0	0	1.359	2	0
1	15.426	0	0	0.77452	2	0
2	0	100	1	0	1	1
2	1.9734	0	0	3.5815	2	0
2	4.0999	0	0	2.4303	2	0
2	6.3688	0	0	1.1134	2	0
2	7.8599	0	0	1.8294	2	0
2	11.442	0	0	.	2	1
2	17.013	0	0	0.26225	2	0

ID: unique subject identification number
TIME: time since first dose
AMT: amount of drug administered
EVID: 1 for dosing, 0 for observation
DV: concentration in this case
CMT: compartment, here 1 for dosing depot and 2 for central compartment (where plasma concentration is measured)
MDV: is the observation missing, e.g. not collected or BLOQ? 1 for yes and 0 for no.

DRUG X: DATA EXPLORATION

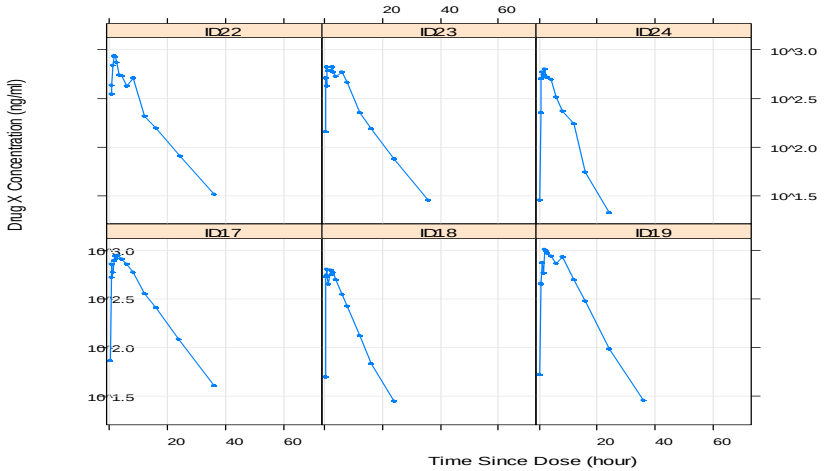




- Different color for different doses
- Studies 1, 2, 3, 101 and 103 are clin pharm studies
- Studies 201, 202 and 302 are Phase II and III studies

DEFINE THE STRUCTURE MODEL

- How many compartments (excluding absorption related)?
  - visual inspection in log scale
  - comparing different models and compare goodness of fit
- Any signs of nonlinearity in dose or time?
  - saturation in absorption
  - saturation in clearance
  - target-mediated drug disposition
  - auto-inhibition or auto-induction
- Absorption process can be complicated and erratic
  - first-order
  - mixed zero-order and first-order
  - enterohepatic recirculation
  - transit –compartment model
  - weibull function
- Define parameters
  - macro-parameters like Vc, Vp, CL, Q
  - micro-constant like kel=CL/Vc, k12=Q/Vc, k21=Q/Vp



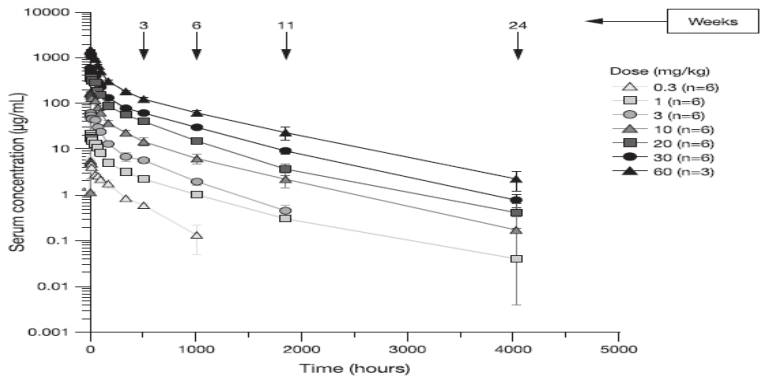
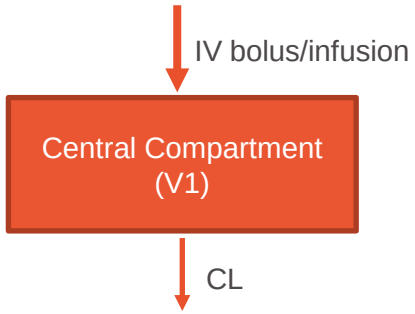


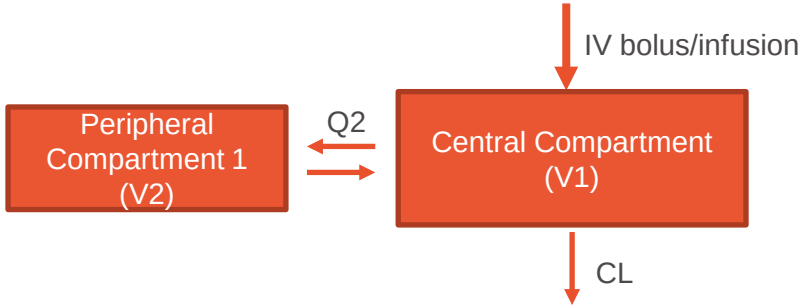
Fig. 1. Serum concentration (mean ± SE) of aducanumab (logarithmic scale) over time after a single dose. [a]One patient in the 10 mg/kg group had a measurable concentration of aducanumab at the pre-dose sample (0) time. Abbreviation: SE, standard error.

STRUCTURE MODEL FOR IV ROUTE

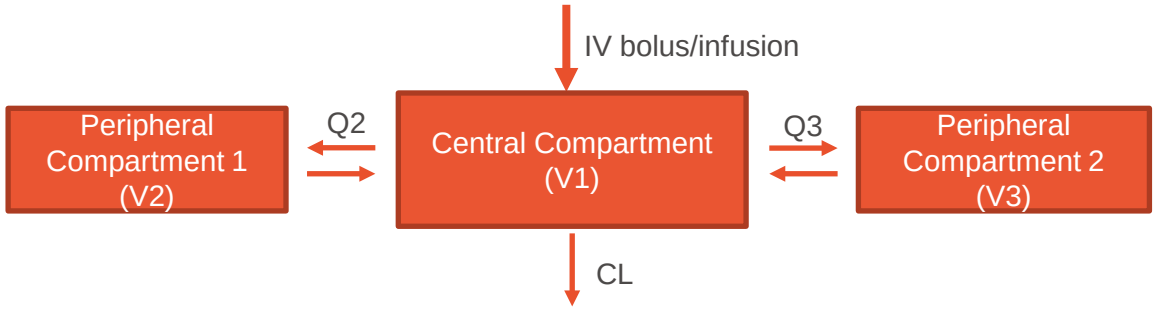
One-compartment model



Two-compartment model

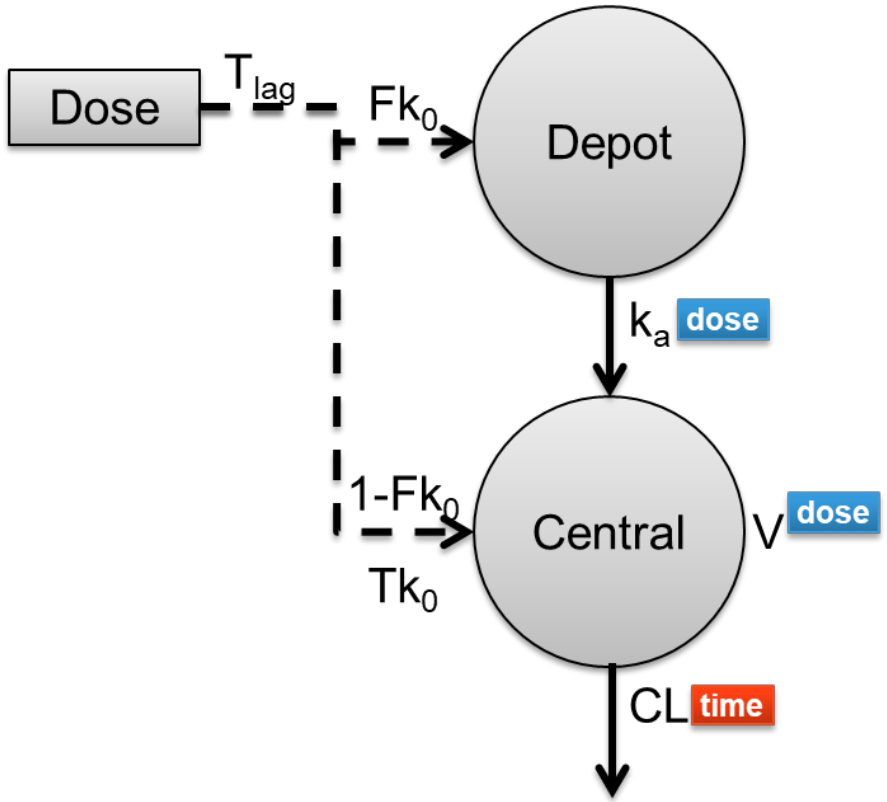


Three-compartment model

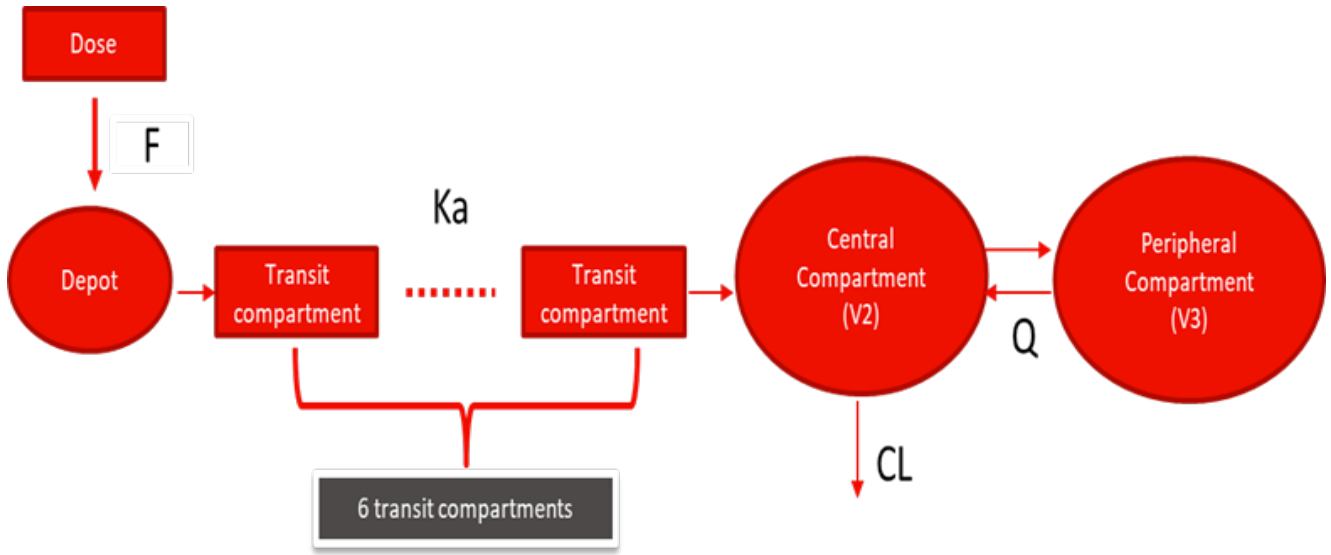


STRUCTURE MODEL FOR PARENTERAL ROUTE

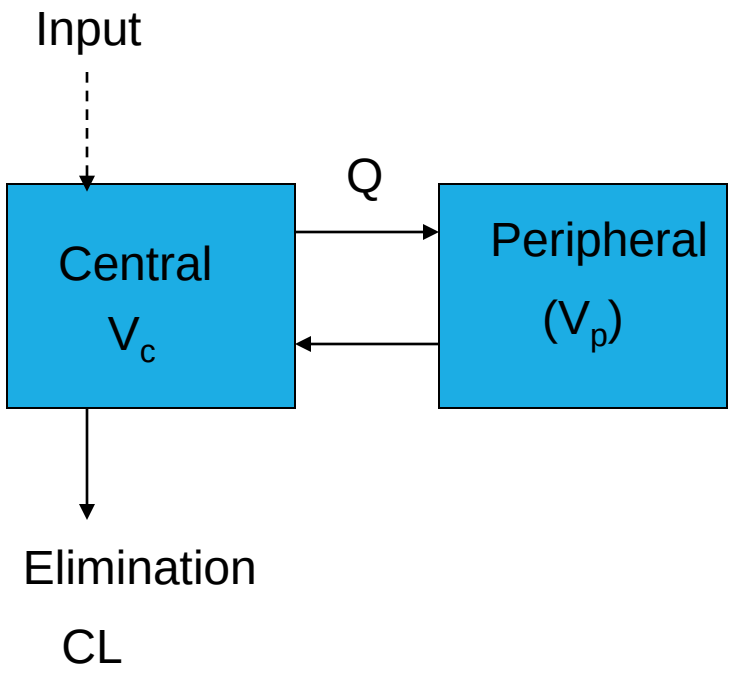
Mixed First- and Zero-order absorption



Transit-compartments for absorption



FIRST-ORDER 2-COMPARTMENT MODEL IV DOSE (DIFFERENTIAL EQUATION)



$$\frac{dA_c}{dt} = k_{21}A_p - (k_{12} + k_{10})A_c$$

$$\frac{dA_p}{dt} = k_{12}A_c - k_{21}A_p$$

$$C_c = A_c/V_c$$

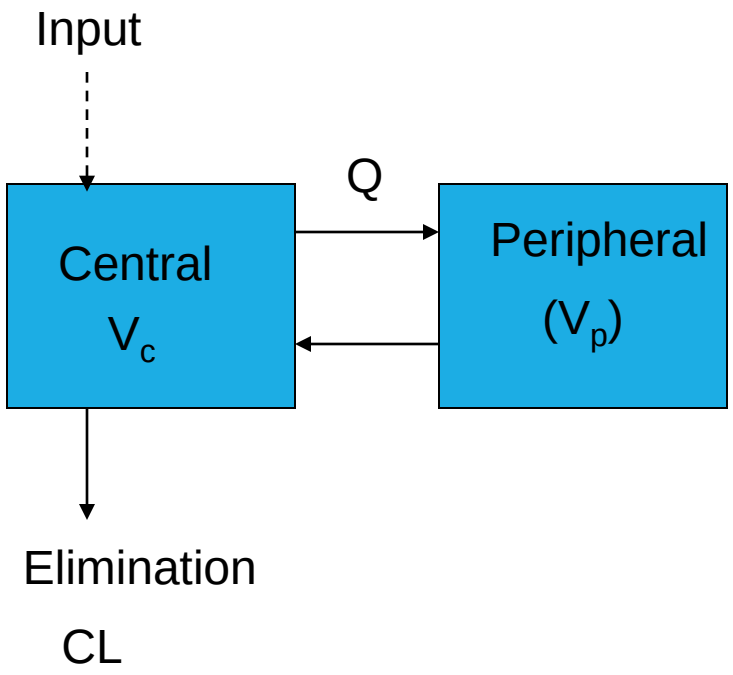
$$A_c(t = 0) = \text{Bolus Dose}$$
$$A_p(t = 0) = 0$$

$$k_{12} = \frac{Q}{V_c}$$

$$k_{21} = \frac{Q}{V_p}$$

$$k_{10} = \frac{CL}{V_c}$$

FIRST-ORDER 2-COMPARTMENT MODEL IV DOSE (CLOSED FORM SOLUTION)



$$k_{12} = \frac{Q}{V_c}$$

$$k_{21} = \frac{Q}{V_p}$$

$$k_{10} = \frac{CL}{V_c}$$

$$a = k_{12} + k_{21} + k_{10}$$

$$\lambda_1 = \frac{a + \sqrt{a^2 - 4k_{10}k_{21}}}{2}$$

$$\lambda_2 = \frac{a - \sqrt{a^2 - 4k_{10}k_{21}}}{2}$$

$$C_1 = \frac{k_{21} - \lambda_1}{\lambda_2 - \lambda_1} / V_1$$

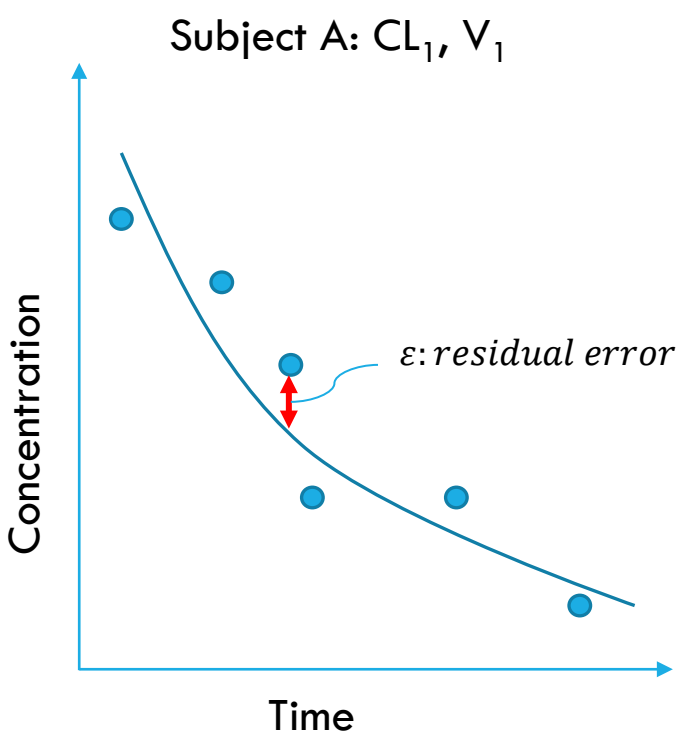
$$C_2 = \frac{k_{21} - \lambda_2}{\lambda_1 - \lambda_2} / V_1$$

Closed form solution for bolus dose: $C(t) = Dose \times (C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t})$

DEFINE THE STOCHASTIC MODEL FOR RANDOM EFFECT AND RESIDUAL ERROR

- Typically the PK parameters are assumed to follow log-normal distribution as they have positive values and skewed to the right
- In theory each of the parameter has inter-subject variability, however depends on relative position of samples on the PK curve, data usually contains more information on some parameters like clearance and volume of central compartment, but less information on parameters like inter-compartment clearance and peripheral compartment volume
- Usually starting a model with random effect on all parameters lead to parameter identifiability issue, suggest to start with simple model and add random effect gradually
- Random effects may be correlated
- Residual errors typically are assumed to be additive error, proportional error, or additive plus proportional error

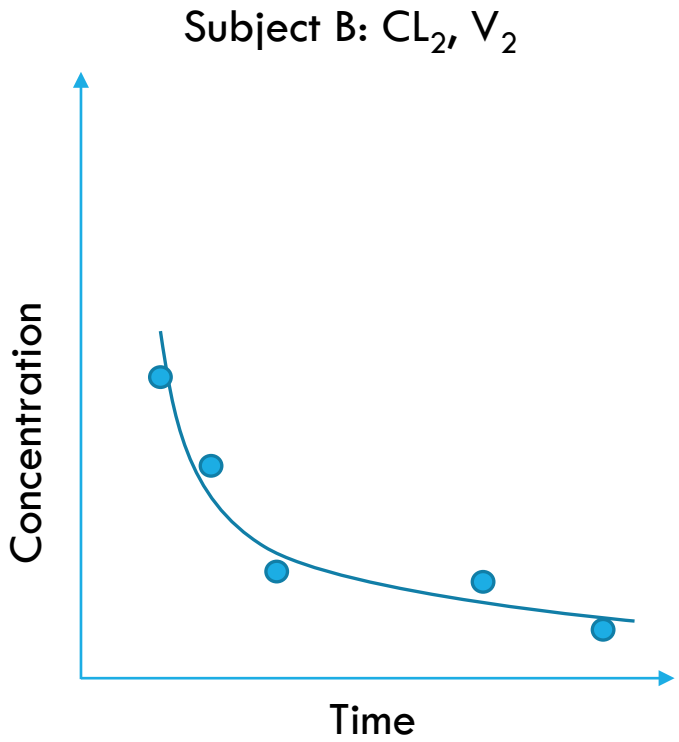
RANDOM EFFECT AND RESIDUAL ERROR



$$Conc(t) = \frac{Dose}{V}\exp(-\frac{CL}{V}*t) + \varepsilon$$

$$\begin{pmatrix} CL \\ V \end{pmatrix} \sim LN\left\{\begin{pmatrix} \mu_1 \\ \mu_2 \end{pmatrix}, \begin{pmatrix} \sigma_{11} & \sigma_{12} \\ \sigma_{21} & \sigma_{22} \end{pmatrix}\right\}$$

CL and V are parameters with ***Random Effect***, and they follow ***Bivariate Log-Normal Distribution***



PARAMETER ESTIMATION

- Objective function value (OFV): proportional to the sum of squared differences of the observations from the model prediction
- OFV is non-linear in model parameters (structure model, random effect and residual error related parameters), estimation of parameter is a process of locating parameter set in parameter space that minimize OFV
- Estimation methods: first order (FO), FO conditional estimation, Laplace method, Monte Carlo importance sampling expectation maximization, Markov Chain Monte Carlo stochastic approximation expectation maximization, Iterative two stage, MCMC Bayesian analysis
- Covariance step for precision of parameter estimates
- Choice of initial value is important, need to avoid parameter estimates being local minima instead of global minima

COVARIATE EFFECT ON PK PARAMETERS

- Covariate effect refers to systemic relationship between PK parameter and covariate, e.g. impaired renal function leads to smaller clearance, allometric scaling
- Covariate effect accounts for between-subject variation and enables us to reduce exposure variation in population or reach desired effect through adjustment on dosing
- Covariates can be continuous (e.g. body weight) or categorical (e.g. sex)
- Need sufficient range for continuous variable and sample size for definitive assessment of covariate effect
- Statistical significance – change in **Objective Function Value**
- Clinical relevance – magnitude of effect, reduction in between-subject variation, degree of change in exposure across range, degree of change in clinical response

PARAMETERIZATION OF COVARIATE EFFECT

- Continuous variable, e.g.
  - Linear: $CL = TVCL + \theta * (age - 50)$
  - Power function: $CL = TVCL * \left(\frac{age}{50}\right)^{\theta}$
  - Other functions like Emax, logit, piece linear functions
- Categorical variable
  - $CL = \begin{cases} \theta_1, & if\ male \\ \theta_2, & if\ female \end{cases}$
- Sometimes, the covariate change with time, e.g., weight-lose drug change body weight which in turn change CL and V, development of anti-drug antibody over time

COVARIATE MODELING

- Identify candidate covariates, biological relevance (e.g. height vs. shoe size, body weight, BMI or lean body weight)
- Evaluate range of covariates and correlation between covariates (to avoid collinearity), sample size
- Screening: plot Empirical Bayesian Estimate of each parameter or random effect against covariates
  - identify covariates to be formally tested in the model
  - identify proper candidate parameter-covariate relationship (some should be based on knowledge of biology, physiology and allometric principles)
  - be aware of shrinkage issue

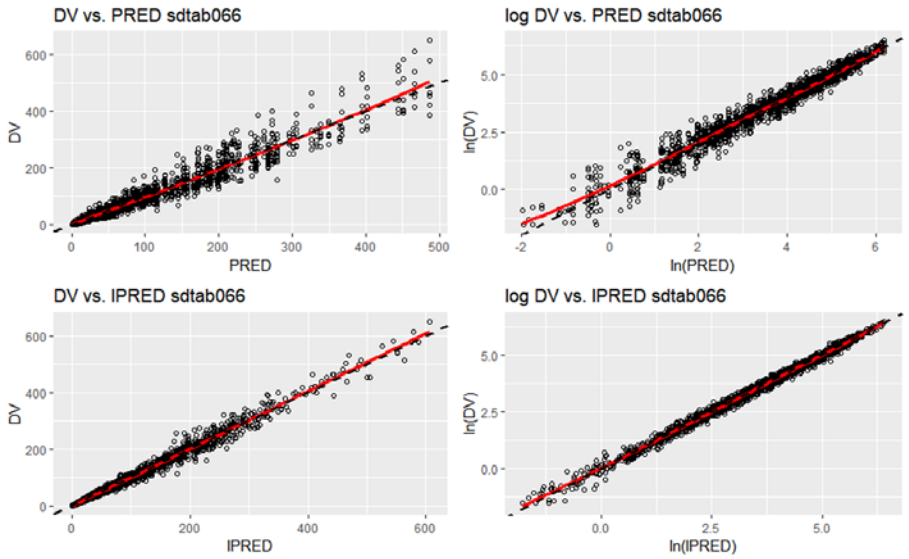
COVARIATE MODELING (CONT'D)

- Covariate selection
  - forward-selection followed by back-ward elimination (use difference p-value for significant criteria)
  - full model followed by back-ward elimination
- Consideration for final inclusion in the model and interpretation
  - magnitude and significance
  - how much between-subject variation does it explain?
  - what is the clinical implication?

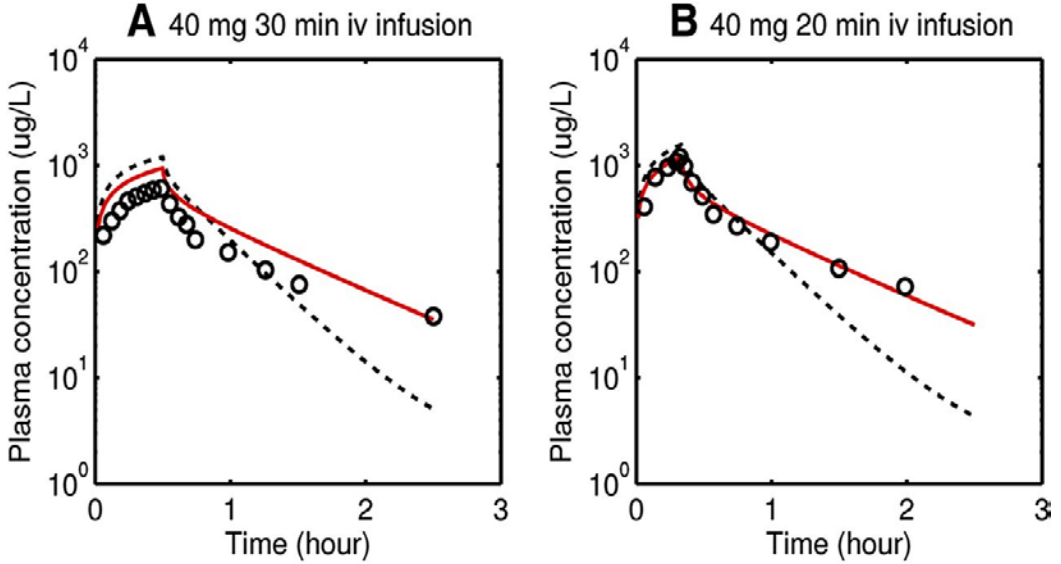
MODEL EVALUATION – THE OBVIOUS ONES

- ❑ Any error/warning message?
- ❑ Was the minimization step successful? Covariance step successful?
- ❑ Are the estimated parameter values plausible from a physiological point of view?
- ❑ Are the parameters estimated with reasonable precision (Relative Standard Error < 30%)
- ❑ Any shrinkage issue?

MODEL EVALUATION – GOODNESS OF FIT

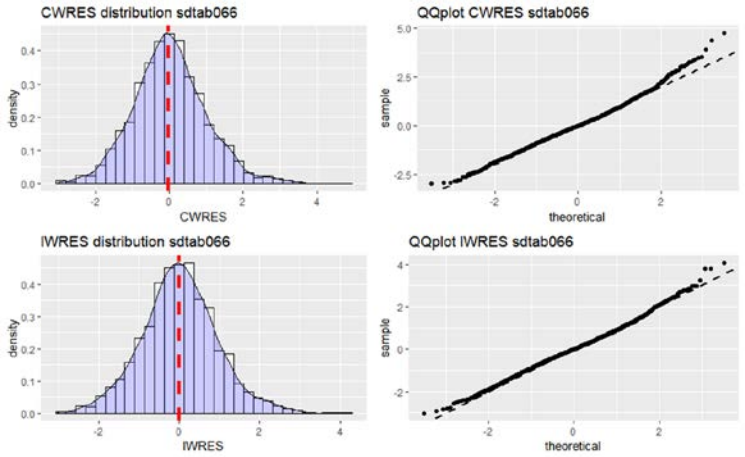


Observed value and model prediction (population prediction, individual prediction) symmetrically scattered around unit line

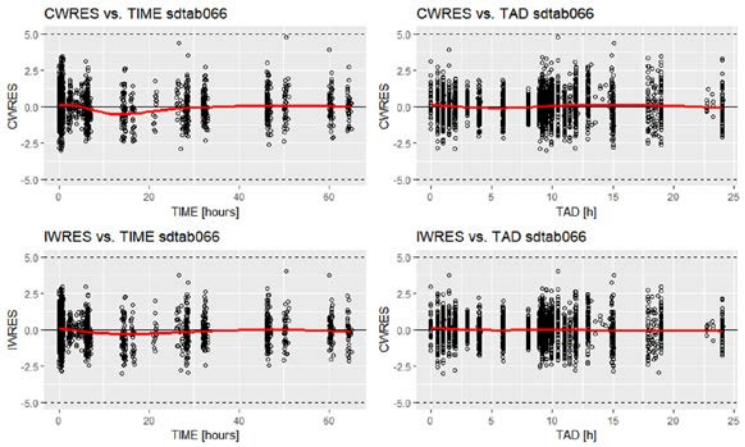


Model prediction should agree with observations

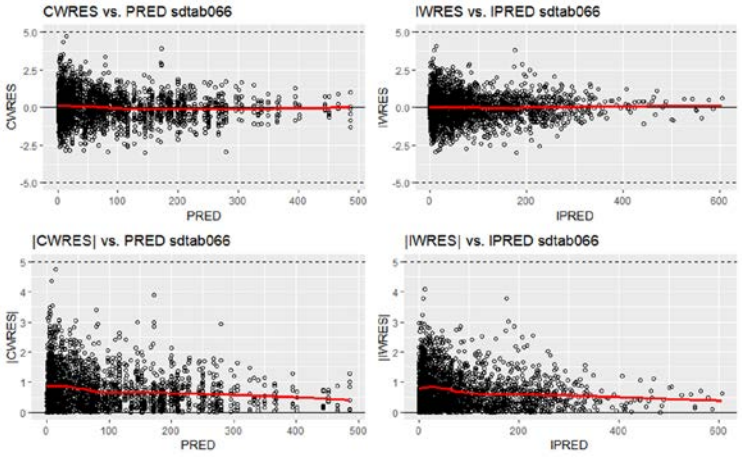
MODEL EVALUATION – WEIGHTED RESIDUAL



Residual errors resemble normal distribution



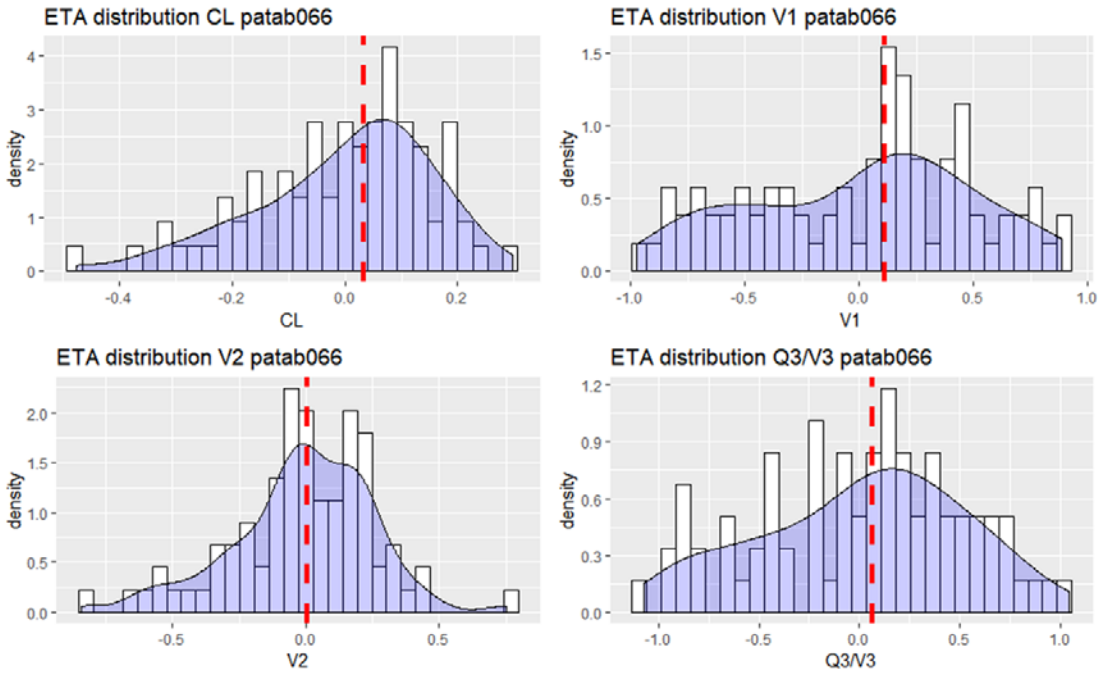
No trend when residual errors plotted against time and within range expected for standard normal distribution



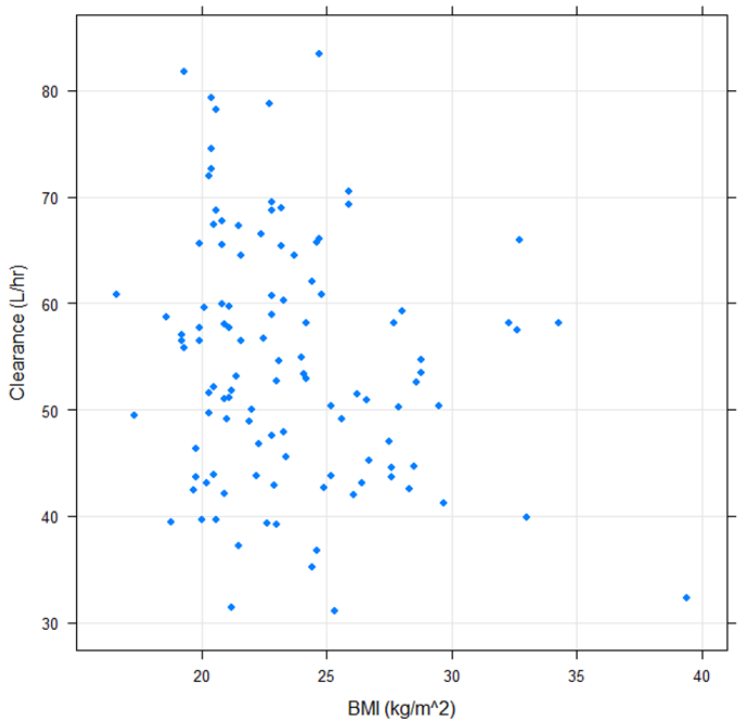
No trend when residual errors plotted against model prediciton and within range expected for standard normal distribution

MODEL EVALUATION – RANDOM EFFECT

Histogram of random effect should look like normal distribution

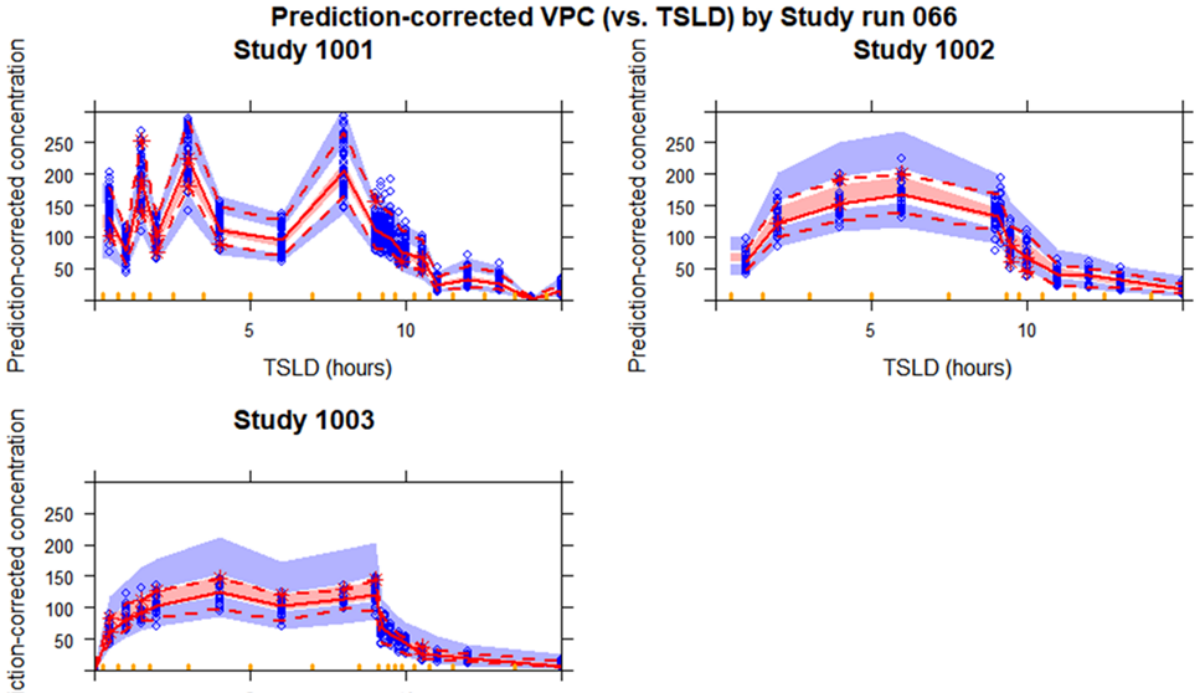


Random effect should lack correlation after covariate step

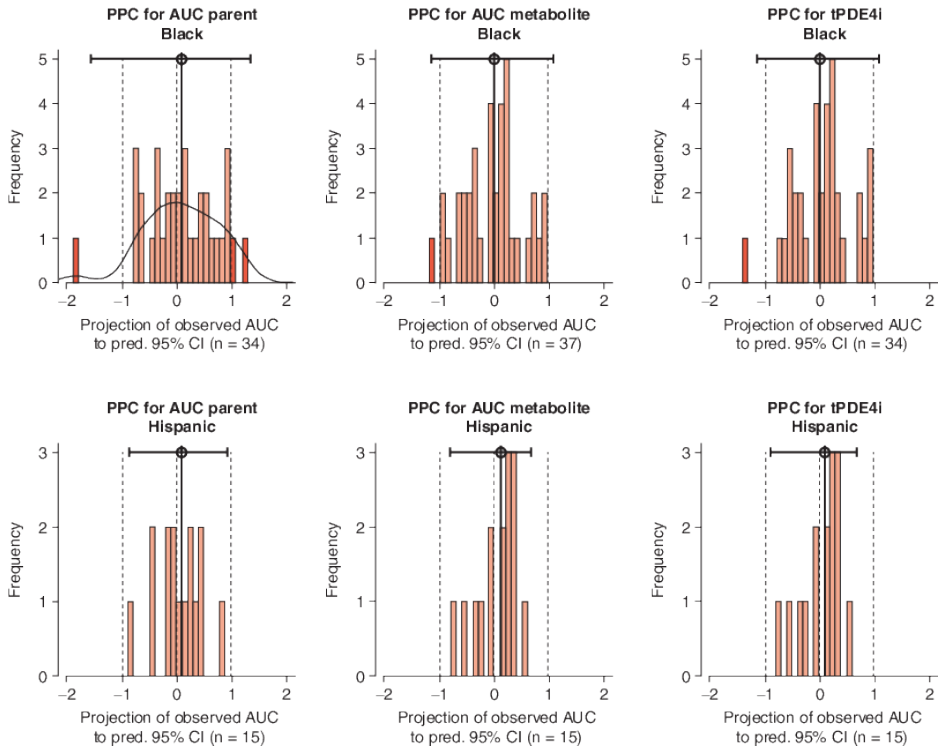


MODEL EVALUATION – SIMULATION BASED

Visual Predictive Check



Posterior Predictive Check



MODEL EVALUATION – OTHER TOPICS

- Bootstrap for parameter confidence interval
- Condition number
- Likelihood profiles
- External validation
- Sensitivity analysis of outliers
- Understand limitation of the model

SIMULATION BASED ON POP PK MODEL

- Question to be addressed
- Type of simulations
  - Typical profile
  - Range of exposure across a population (random effect)
- Simulation design
  - Dose regimen
  - Sampling time points
  - Number of subjects
  - Realistic distribution for covariates
- Choice of parameters
  - Final estimate
  - Uncertainty in parameter estimates
  - Correlation between parameters

OTHER TOPICS RELATED TO POP PK MODELING

- Optimization of sampling scheme
- Handling of LLOQ data
- Identification of outliers and how to handle them
- Software
  - Parameter estimation: NONMEM, Monolix, NLME in S-plus, R packages, NLME in Phoenix, etc
  - Post-processing: R, Xpose, Perl-speaks-NONMEM
  - Work bench: KIWI, Pirana
- Model should be fit-for-purpose
- The law of briefness – parsimonious model

Case Study

TAPENTADOL: POP PK TO FACILITATE DOSE SELECTION IN PEDIATRIC POPULATION

Background

- Tapentadol is a centrally acting strong analgesic that acts through μ-opioid receptor agonism and noradrenaline reuptake inhibition
- Infants and children of all ages (including neonates) are able to perceive and experience pain
- Approved dose in adult 50-100 mg every 4-6 hours
- Two postsurgical studies with single dose of Tapentadol in pediatric population were conducted with PK collection
- Need to identify dose regimen to be tested in a confirmatory efficacy study in 2-18 year old patients suffering from acute postsurgical pain

Strategy

- Develop Pop PK with covariates based on two pediatric PK studies
- Simulate dose regimens that yields exposure similar to approved dose regimens in adults

TAPENTADOL PEDIATRIC PK STUDY

- Two single-dose phase 2 trials evaluating PK profile, safety and efficacy of tapentadol oral solution for the treatment of postsurgical pain in children and adolescents
- Sampling scheme:
  - 12 to <18 years: 8 venous samples at 0.25, 0.5, 1, 2, 4, 6, 11 and 15 hrs
  - 6 to <12 years: 4 venous samples within 4 time windows of 0.25-1, 1-4, 4-11, and 11-15 hours
  - 3-5 years: 2 venous samples within 2 time windows of 0.25 -1, 4-11 hours
  - 2 years: 1.25, 3, 5 and 8 hours

Table 1 Age, bodyweight, and sex (% females) of the trial populations

	Age (years)	Bodyweight (kg)	% females
NCT01729728 (n=56)[17]			
12 to <18 years (n=19)	16 (12–17)	60.8 (43.5–79.7)	42.1
6 to <12 years (n=22)	8 (6–11)	29.05 (21.8–44.9)	68.1
2 to <6 years (n=15)	3 (2–5)	16.3 (12.7–19.5)	46.7
NCT01134536 (n=36)[16]			
12 to <18 years (n=25)	14.5 (12–17)	59 (41–80)	52.0
6 to <12 years (n=11)	9 (6–11)	31 (20.2–58)	54.5
Combined (n=92)			
12 to <18 years (n=44)	15 (12–17)	60 (41–80)	47.7
6 to <12 years (n=33)	9 (6–11)	29.5 (20.2–58)	63.6
2 to <6 years (n=15)	3 (2–5)	16.3 (12.7–19.5)	46.7

Note: Data are median (range).

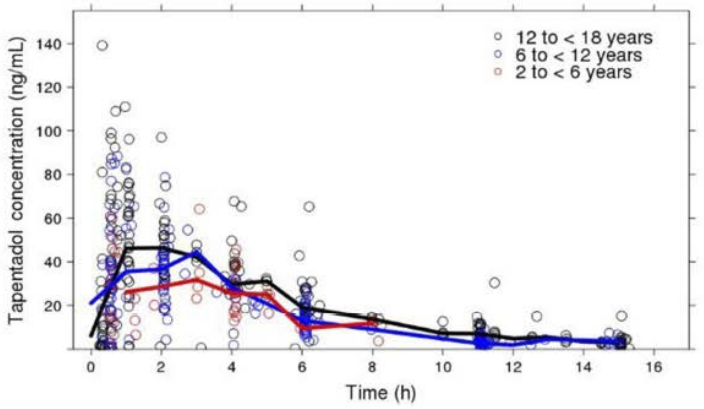


Figure 1 Scatter plot of observed tapentadol concentration versus time. The open circles represent the observed tapentadol concentrations and the lines represent the median concentrations.

TAPENTADOL POP PK MODEL

- Structure model: both 1- and 2- compartment models are tried and 1-compartment model with linear clearance and first-order absorption is adequate
- Random effect model: $P_i = P_{tv} \times \exp(\eta_i)$
- Residual error model: $C_{o,ij} = C_{p,ij} \times (1 + \varepsilon_{1,ij}) + \varepsilon_{2,ij}$
- Covariate model: $P_{TV} = \theta \times \left(\frac{X}{X_{ref}}\right)^n$, $P_{TV} = \theta_{ref} \times (1 + \sum \theta_j * I)$
- Covariates included in base model: body weight on CL/F and V/F
- Candidate covariates: age, sex, aspartate transaminase (AST), alanine transaminase (ALT), alkaline phosphatases (ALP) and bilirubin on CL/F and V/F, creatinine clearance (CRCL) on CL/F

TAPENTADOL FINAL POP PK MODEL

Table 2 Final tapentadol population pharmacokinetics parameter estimates and 95% confidence intervals. Estimates of CL/F and V/F relate to a reference weight of 45 kg

Parameter	Estimate	RSE (%)	95% Confidence interval	
			NONMEM	Bootstrap (n=500)
CL/F (L/h)	170	3.3	159.06–180.94	162.08–182.94
V/F (L)	685	4.5	624.83–745.17	653.55–777.96
Ka (h^{-1})	2.03	16.5	1.373–2.687	1.599–3.263
TLAG (h)	0.247	0.7	0.243–0.251	0.245–0.273
Exponent CL-WT	0.638	11.1	0.499–0.777	0.515–0.766
Exponent V-WT	0.847	10.2	0.678–1.016	0.718–1.029
Additive error (ng/mL)	0.181	39.1	0.042–0.32	0.036–0.415
Proportional error (σ)	0.329	8.7	0.273–0.385	0.269–0.365
IIV CL/F (ω^2)	0.048	32.1	0.018–0.078	0.025–0.088
IIV V/F (ω^2)	0.024	61.5	−0.005–0.053	0.012–0.081
IIV Ka (ω^2)	1.99	32.2	0.734–3.246	1.042–3.673
Cov CL/F-V/F	0.03	46.1	0.003–0.057	0.012–0.071
Cov CL/F-Ka	0.009	614.5	−0.107–0.126	−0.090–0.155
Cov V/F-Ka	−0.072	93.6	−0.203–0.060	−0.219–0.080

Abbreviations: CL/F, apparent clearance after OS administration; Cov, covariance; σ, standard deviation; ω^2, variance; IIV, inter-individual variability; Ka, first-order absorption rate constant; RSE, relative standard error (derived from the covariance matrix of the estimates reported by NONMEM); TLAG, absorption lag-time; V/F, apparent volume of distribution after OS administration; WT, weight.

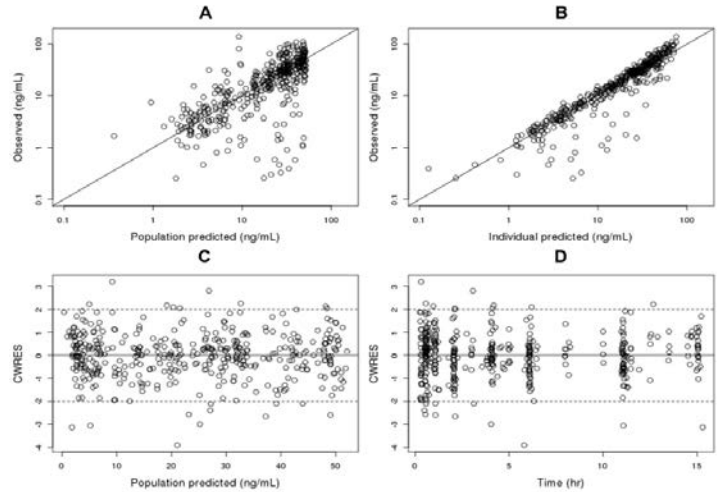


Figure 2 Plot of observed tapentadol concentration versus population predicted (**A**), observed tapentadol concentration versus individual predicted (**B**), conditional weighted residuals versus population predicted (**C**), conditional weighted residuals versus time (**D**). The black represents the identity line (**A, B**) or the zero line (**C, D**).
Abbreviation: CWRES, conditional weighted residuals.

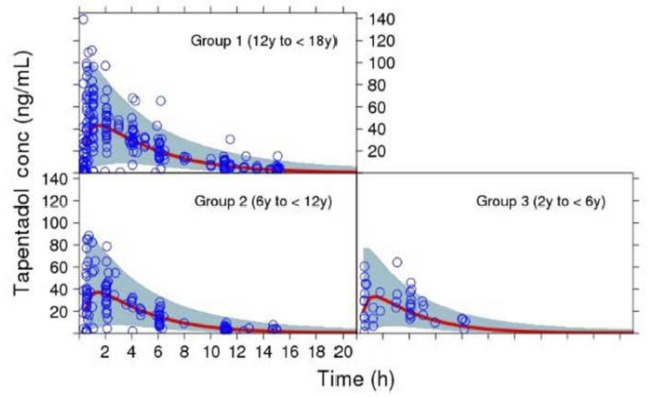


Figure 3 Simulated concentration-time curve for the pediatric population (2 to <18 years) using final parameter estimates from the population pharmacokinetic model, showing the variability (blue area, representing the 95% prediction interval) and central trend (red line: median prediction), together with the observations (open circles).
Abbreviation: y, years.

DOSE RECOMMENDATION FOR TAPENTADOL BASED ON FINAL POP PK MODEL

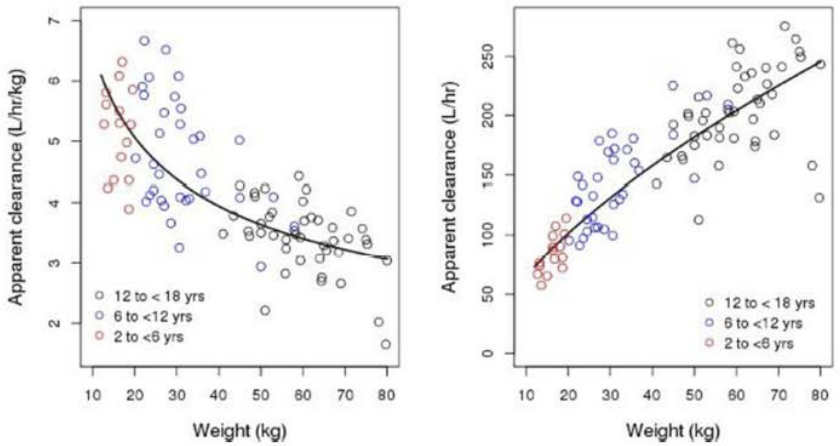


Figure 5 Empirical Bayesian estimates of bodyweight-normalized apparent clearance (left panel) and apparent clearance (right panel) versus weight together with modeled relationship, using a power function (line) (Table 2).
Abbreviations: AUC, area under the curve; yrs, years.

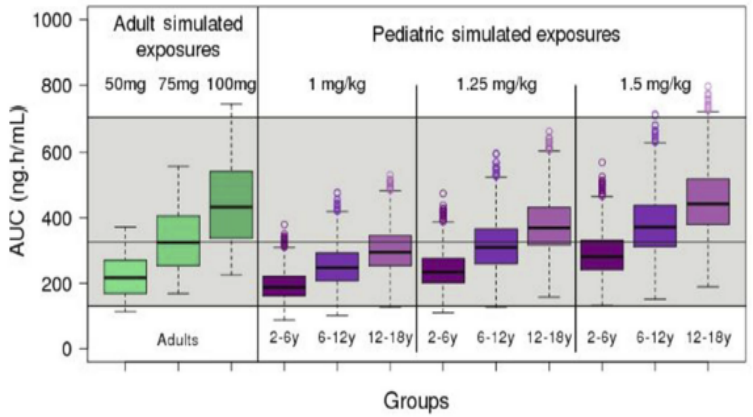
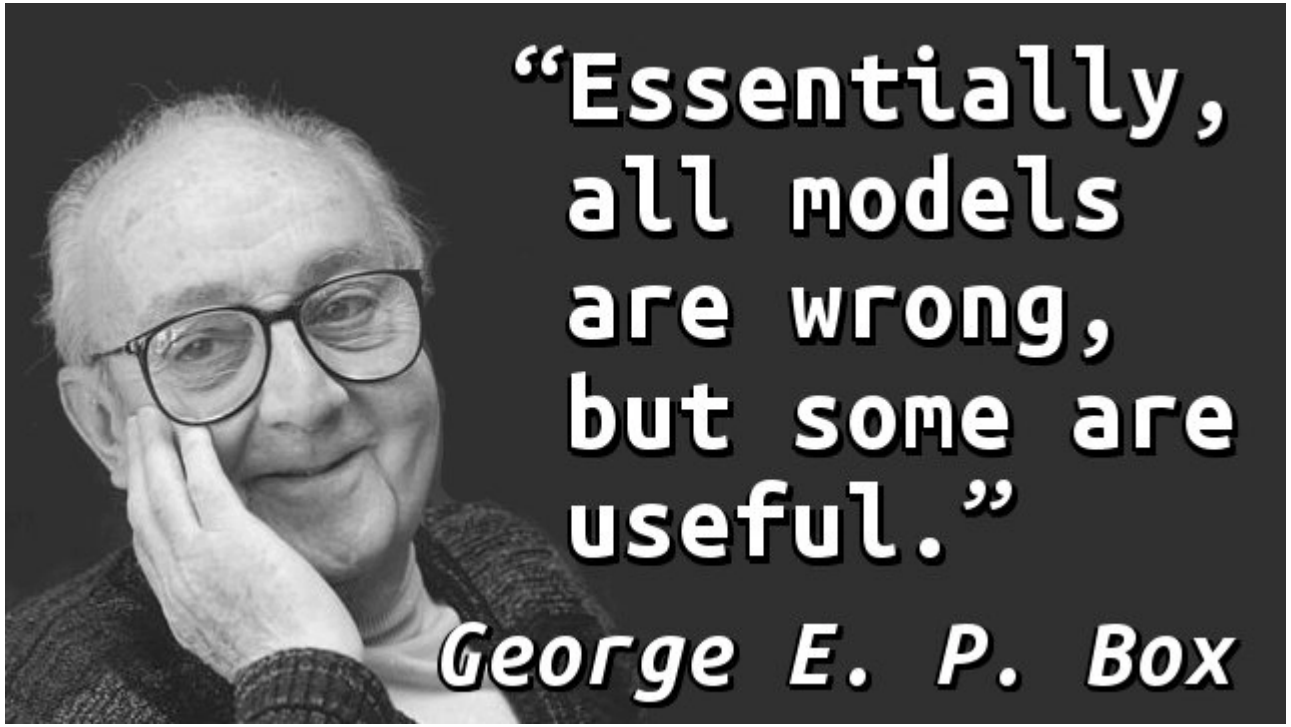


Figure 4 Boxplot of the simulated steady-state area under the curve (AUCss) of tapentadol in adults and pediatric subjects 2 to <18 years of age receiving 1.0 mg/kg, 1.25 mg/kg, and 1.5 mg/kg of tapentadol every 4 hrs. The gray shaded area represents the 2.5th and the 97.5th percentile of the AUCss in adults receiving 50 mg and 100 mg tapentadol every 4 hrs, respectively. The central black line indicates the 50th percentile (median) of the AUC in adults receiving 75 mg tapentadol every 4 hrs.
Abbreviations: AUC, area under the curve; y, years.

- Clearance increases with body weight, however body weight normalized clearance decrease with weight, which explains why a body weight based dosing regimen do not yield same exposure range across age groups
- Recommended dose regimen for pediatric confirmatory study: 1.25 mg/kg every 4 hours, which best mimic exposure (AUCss) range as approved dose range 50-100 mg

LET'S GO MODELING!!!



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Thank You and Questions