Sensitivity analysis to help the assessment of variance : Application to Target Mediated Drug Disposition (TMDD) PK/PD model describing the effect of a monoclonal antibody (mAb) on a circadian biomarker

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Introduction and Objectives

•To assess the variance (interindividual variability, IIV) parameters of the PKPD model using a sensitivity analysis.
•To describe, using the model, the change of the biomarker input rate following administration of the mAb.

Material and Methods

• ~ 10 PK and 9 PD data per individual were available over a time frame of 2 weeks (or more).
•Multi-compartments PK models with non-linear TMDD clearance were fit to the mAb serum concentration versus time data (Gibiansky et al, 2008, 2009).
•An indirect response PKPD model, with a sigmoid Emax function describing the effect of the mAb on the input rate of the biomarker, was fit to the pharmacodynamic (biomarker) data.
•To account for the biomarker circadian rhythmic change, this model also included a cosine function to describe the input rate of the biomarker.
•A two stage approach was followed where the PK parameters were fixed for the estimation of the PD model's parameters.
•NONMEM version VII.2 was used to model the data with the First Order Conditional Estimation with Interaction (FOCEI) method. Visual predictive checks (VPC), standard error on the estimates, objective function values and diagnostic plots were used to drive the model development.

Results

•A three-compartment PK model with non-linear TMDD clearance adequately fit the mAb PK data (figure 2a-2d).
•This model was found to be better than a two compartment model (dOBJF:-41.729) – figures 2a-2f - table 3).
•The model estimated variance (IIV) on clearance was high (66.3 % - table 1) relative to the CV on clearance (40%,OMEGA=0.15) calculated from the standard non-compartmental analysis (NCA).
•VPC on the PK model were performed with either the model estimated IIV on clearance or the IIV fixed to the value from the NCA (figures 2e-2g).
•For the PD model, mean parameters were reliably estimated with standard error on the estimates (SEE) less than 25 % (except for EC50, SEE 34%) (table 2).
• Variance parameters were less precisely estimated than the fixed effects. This issue in the estimation of variances led to inflated distributions in the visual predictive check plots. (figure 3b). Still the median trend in the PD data is well predicted (figures 3a to 3f).
•A sensitivity analysis was carried out on the IIV on the EC50 (figure 3g). The results indicate that the data set do not enable reliable estimation of the IIV on EC50.
•Arbitrary reasonable value for IIV were chosen to draw new VPC (figure 3b).
   •For EC50 CV of 60 % (OMEGA 0.31) rather than CV of 257 % (OMEGA 2.03)
   •The mean parameters were also re-estimated with the IIV fixed to those value and the impact on the goodness of fit investigated (figures 3c-3h).
   (Criteria=100*(PRED-DV)/DV) (figure 2g PK model and 3g PD model).
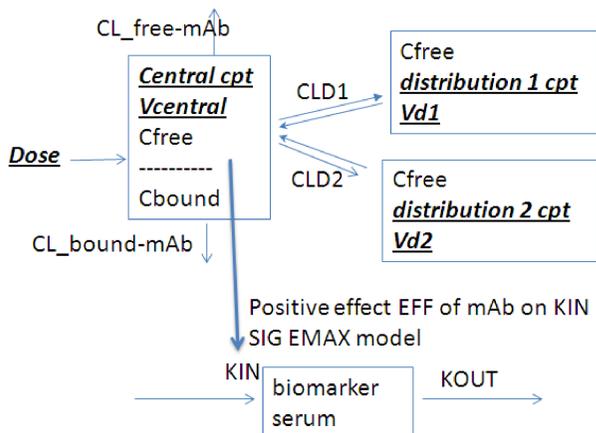•The schematic of the PK model (figure 1) and the differential equations for the PD model are presented below :

Figure 1: schematic representation

Table 1 : PK model parameters results

Parameters Description	Mean	(SEE%)	IIV - CV	(SEE%)
CL_free-mAb (L/h)	0.0307	(19.0)	66.3	(33.2)
CL_bound-mAb (L/h)	0.0618	(22.7)	NC	
Vcentral (L)	2.72	(4.78)	20.2	(36.5)
CLD1 (L/h)	0.0203	(3.96)	NC	
Vd1 (L)	5.37	(4.73)	9.4	(61.1)
CLD2 (L/h)	0.195	(6.82)	NC	
Vd2 (L)	0.591	(17.9)	NC	
KD (nmol/L)	3.97	(15.2)	NC	
RT (nmol/L)	71.3	(7.45)	NC	
Proportional residual error	14.4 % (18.3)			
Additive residual error	+/- 0.0474 nmol/L (19.3)			

Derived parameters t1/2_a, t1/2_b and t1/2_c equal to 1.3, 2.8 and 10.2 days, respectively.
RT = total target concentration ; KD=equilibrium dissociation constant mAb-target complex
Ctot=A(1)/S1
Cfree =((Ctot-RT-KD)+SQRT((Ctot-RT-KD)**2 + 4*Ctot*KD))/2
Cbound=Ctot-Cfree
EL= CL_free-mAb*Cfree + CL_bound-mAb*(Ctot-Cfree)
AA= (CLD1+CLD2)*Cfree
DADT(1) = CLD1*A(2)/Vd1+CLD2*A(3)/Vd2 - EL - AA
DADT(2)=CLD1*Cfree -CLD2*A(3)/Vd1
DADT(3)=CLD2*Cfree -CLD2*A(3)/Vd2

Equation describing KIN, the input rate of biomarker (Figure 4):
   TID1=TICO*2*3.1416)/24
   KIN=(COS(TID1-TIMD)+ KINb) *AMPL
Equation describing EFF , the effect of serum mAb on KIN
   EFF=1+(EMAX*mAb^GAM/(EC50^GAM+ mAb^GAM))
Differential equation for the biomarker
   DADT(biomarker)=KIN*EFF-KOUT*biomarker

TICO = time of the observation in a 24 clock (e.g 12:03) in the data set ; TIMD = parameter of adjustment of time relative to 24 h clock time. AMPL = amplitude of the change in biomarker input rate over the 24 h circadian cycle; KINb = the lowest biomarker input rate over the 24 h circadian rhythm

Table 2 below presents the PD results. Figure 2 (panels a to g) and figure 3 (panels a to h) present the goodness-of-the-fit plots for the PK and PD models respectively

Table 2 : PD model parameters results

Parameters Description	Mean	(SEE%)	CV	(SEE%)
KINb (µmol/L/h)	1.30	(16.5)		
TIMD (h)	3.63	(1.54)		
AMPL (no unit)	1.06	(21.7)	78.5	(70.2)
KOUT (1/h)	0.122	(23.6)	68.3	(75.2)
EMAX (no unit) *100 = % increase (maximum value)	1.02	(18.7)	25.5	(126)
EC50 (µMol)	0.0510	(33.9)	257	(44.2)
GAM (no unit)	1.94	(16.9)		
Residual error	21.0 (15.2)			

Abbreviations: AMPL = amplitude of the change in biomarker input rate over the 24 h circadian cycle; CV = coefficient of variation; EC50 = concentration of mAb leading to increase in biomarker input rate equal to 50% of maximum increase EMAX; EMAX = maximum increase in biomarker input rate in the presence of mAb; GAM = hill coefficient, shape of the sigmoidal effect curve (effect of mAb on biomarker input rate); KINb = the lowest biomarker input rate over the 24 h circadian rhythm; SEE = standard error on the estimated value;
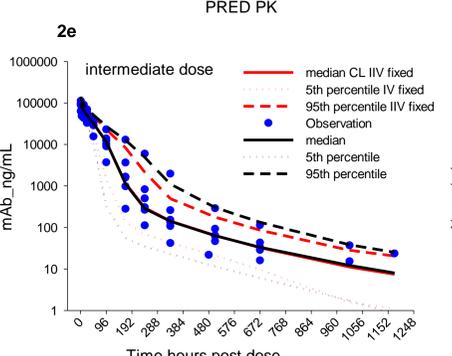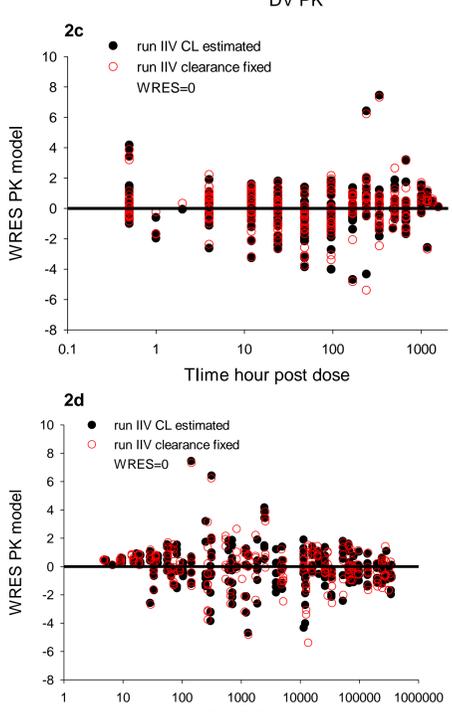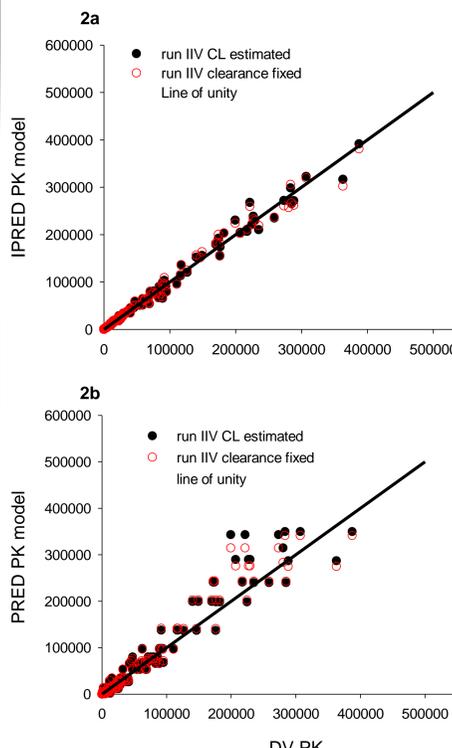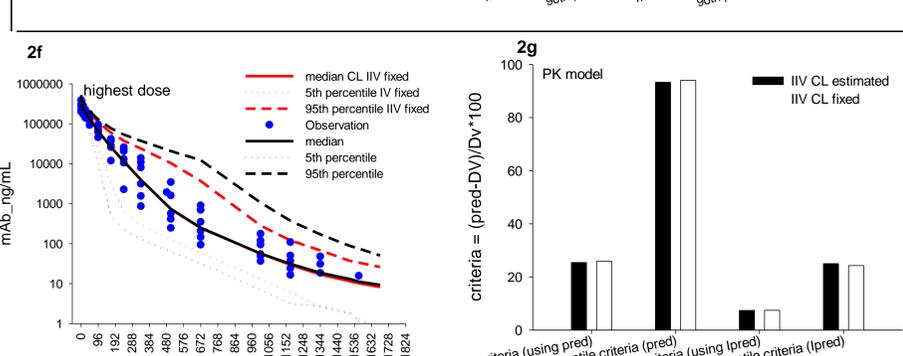
Table 3 : List of the runs

	Run	OBJF
PK	TMDD – 2 compartment model	-398.651
PK	TMDD – 3 compartment model	-440.38
PKPD	IIV on both EMAX and EC50	1184.556
PKPD	IIV on EMAX only	1194.029

Figure 4 : KIN versus mAb Concentration
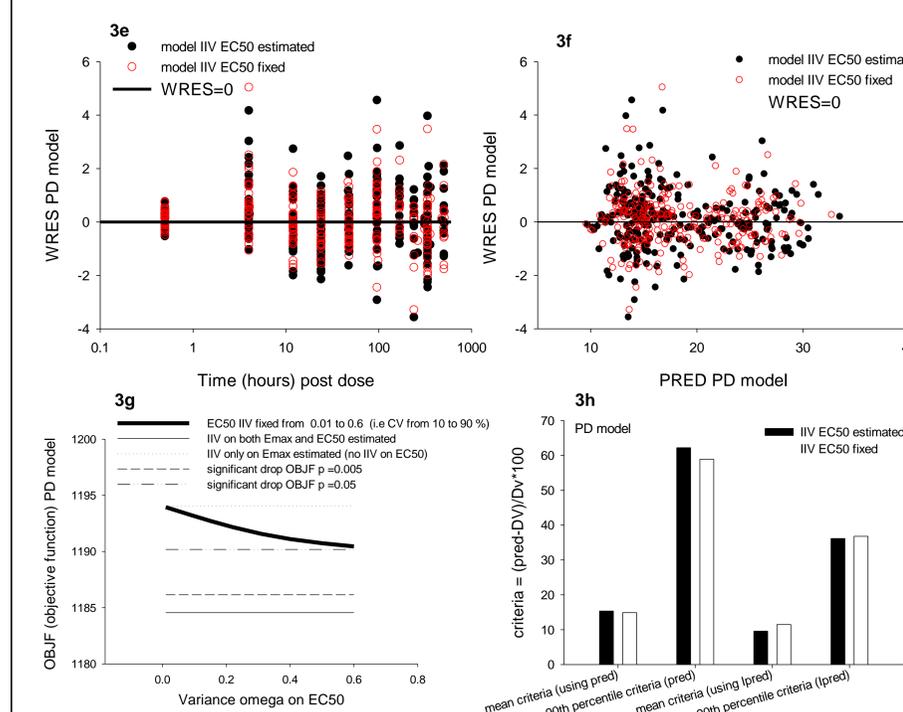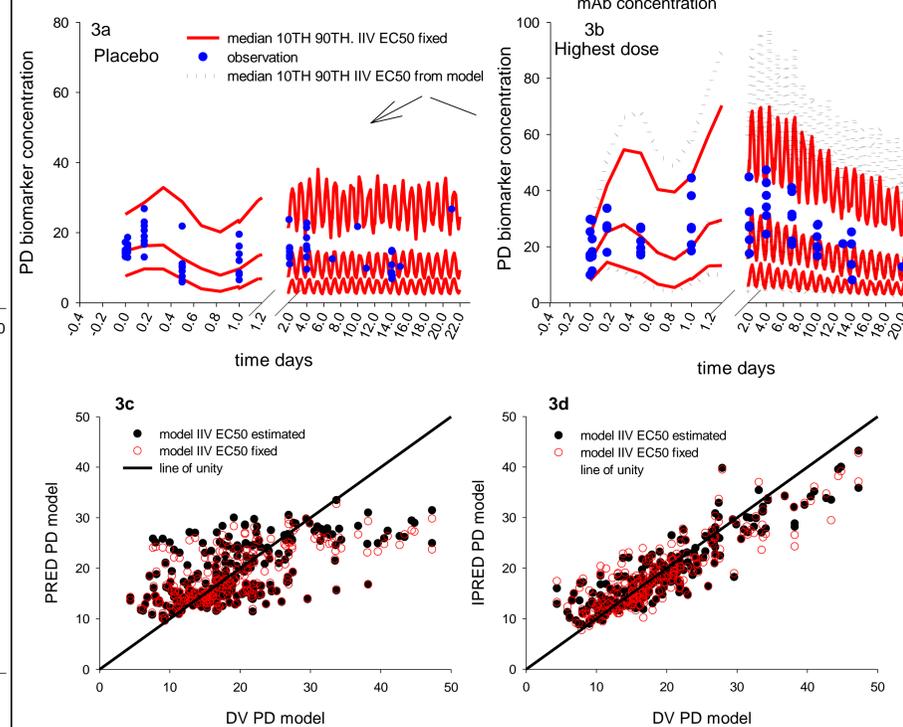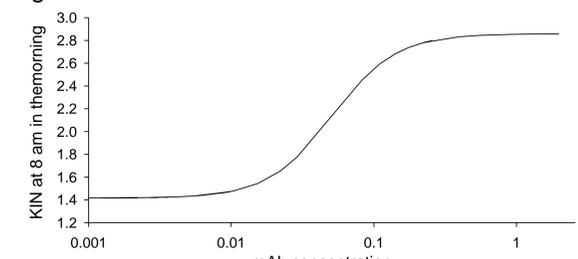
Discussions – conclusions

•In some circumstances (limited numbers of subjects, complex non-linear relationships), the variability (variance) in the model parameters can not be reliably estimated from the data. In those instances, the mean/median trend in the data can be well described however the variability is not. This poster presents a methodology to investigate the impact of fixing the variance parameters to lower value than the model estimate in order to obtain more reasonable description of the variability in the data.
In the example presented :
   •The CV on clearance from the NCA PK analysis lead to a better description (less inflated VPC) of the variability in the mAb concentration data compared to the model estimated IIV-CV on CL (figures 2e-2f).
   •The indirect response PKPD model, adequately described the mean profiles of the biomarker. Sensitivity analysis on the IIV on EC50 enabled to confirm that the data set available could not provide a reliable estimation of that IIV (figure 3g) .
   •VPC for the PD model indicates that the fixed IIV value for EC50 does not lead to worse (compared to estimated IIV) predictions of the PD observations (figure 3c to 3h) and does lead to better description of the overall variability in the PD response figure 3b.

REFERENCES : Gibiansky L, Gibiansky E. Target-mediated drug disposition model: relationships with indirect response models and application to population PK-PD analysis. 2009; J Pharmacokinet Pharmacodyn; 36:341-351.
Gibiansky L, Gibiansky E, Kakkar T, Ma P. Approximations of the target-mediated drug disposition model and identifiability of model parameters. 2008; J Pharmacokinet Pharmacodyn; 35:573-591.

Answers That Matter