



A Mechanism-Based PK/PD Model Predicts the Time-Course of Hematological responses for Epoetin beta

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Objectives

- to develop a Mechanism-Based PK/PD model:
 - to describe the hematological responses in healthy volunteers' study
 - to predict the hematological responses in renal anemia patients' studies
 - to predict not only mean values but also individual values' distribution
 - to predict the responses for different dose routes & different dose frequencies

Outline

- Mechanism of Epoetin pharmacodynamics
- PK/PD modeling with healthy volunteers' study
- Simulation for renal anemia patients' studies

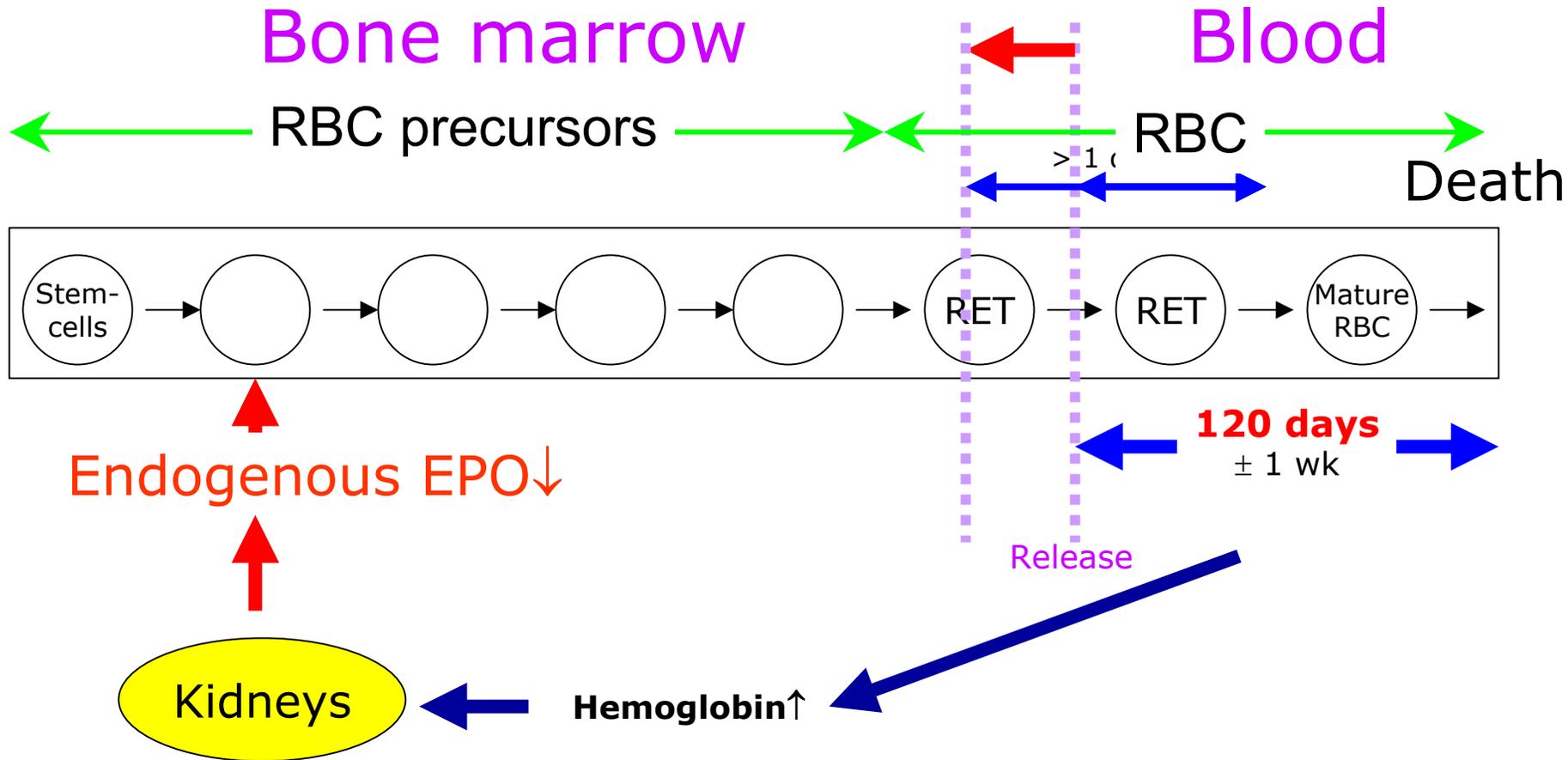
Mechanism of Epoetin pharmacodynamics

Physiological background (1)

- Erythropoietin stimulates the release of RBC (reticulocyte) from Bone Marrow
- Erythropoietin is a glycoprotein produced in the kidneys
- Renal dysfunction patients show anemia because the endogenous EPO production is reduced

Mechanism of Epoetin pharmacodynamics

Physiological background (2)



Mechanism of Epoetin pharmacodynamics

Characteristics of PK/PD model

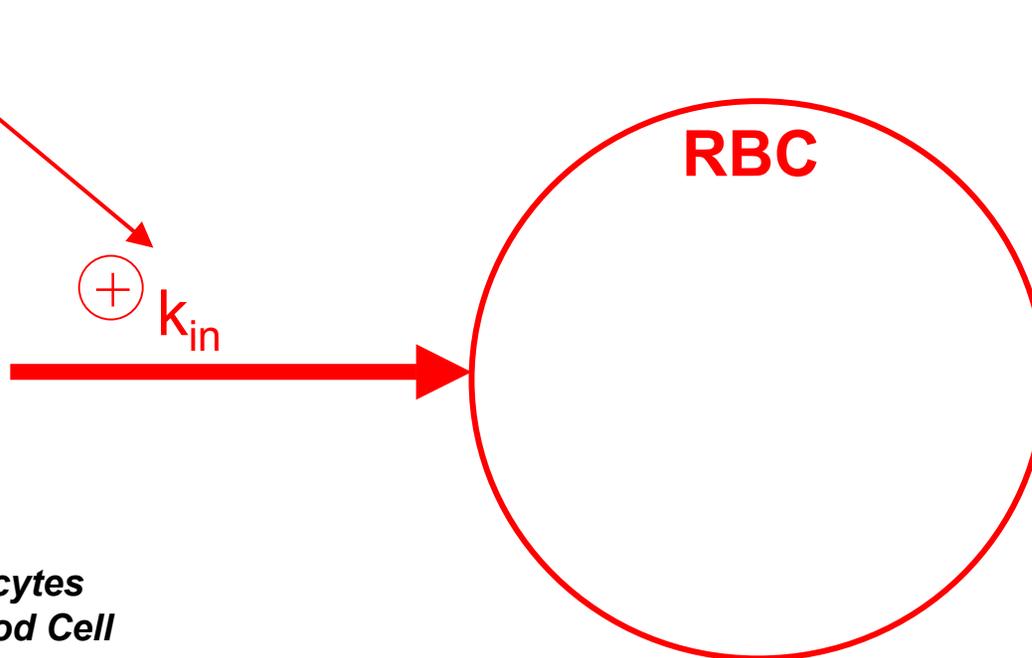
- an identical life span for all RBC (zero order elimination)
- a homeostatic negative feed back
- a lag time
- an indirect response model for reticulocyte with a variable k_{out} (immature reticulocyte increase)
- an E_{max} model with a variable base line
- a blood sampling effect

Mechanism of Epoetin pharmacodynamics

Model equations

$$P'(t) = P_0(t) + \frac{E_{max} \times C_p(t)}{EC_{50} + C_p(t)}$$

**CERA
Concentration**



RET = Reticulocytes
RBC = Red Blood Cell

Mechanism of Epoetin pharmacodynamics

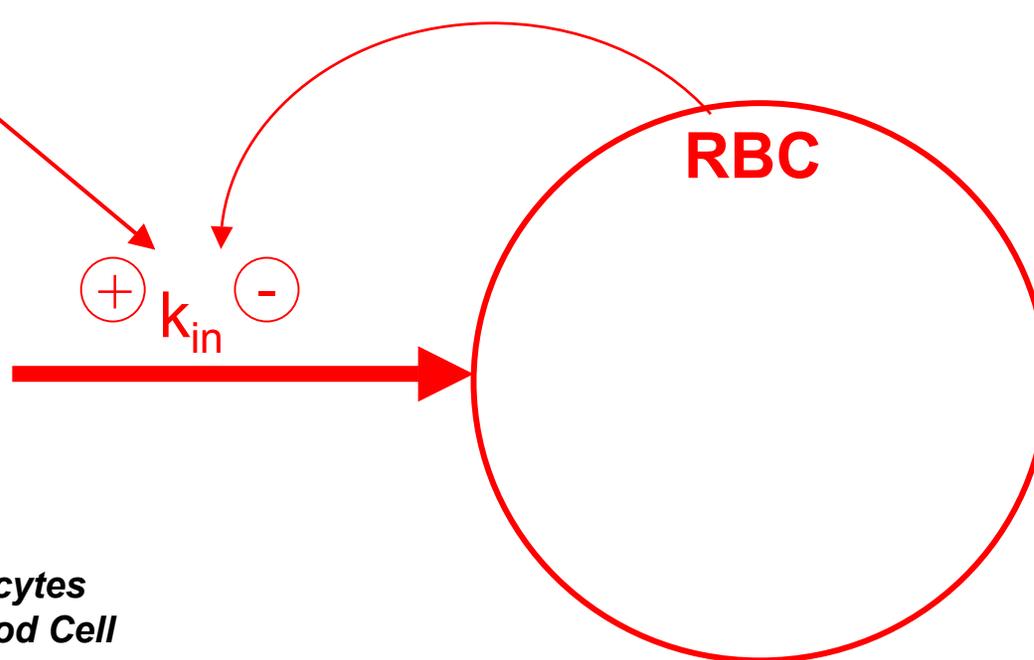
Model equations

$$P_0(t) = \bar{P}_0 \times \exp(- \text{Slope} \times \Delta Hb(t))$$

$$\bar{P}_0 = RBC(0) / SPAN$$

**CERA
Concentration**

**Negative
Feedback**



RET = Reticulocytes
RBC = Red Blood Cell

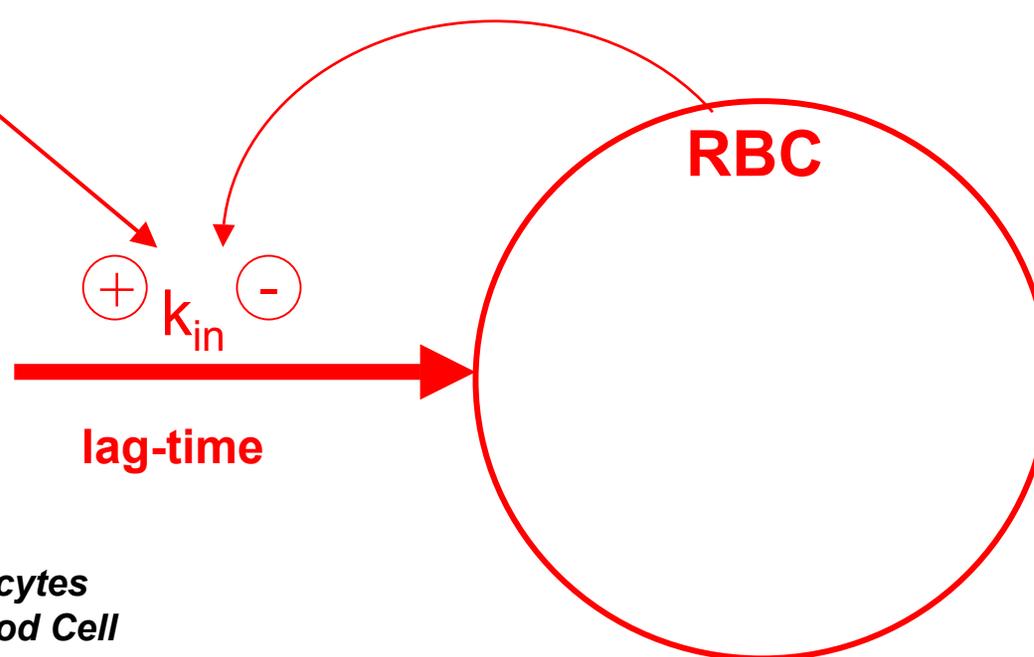
Mechanism of Epoetin pharmacodynamics

Model equations

$$\frac{dP(t)}{dt} = \frac{I}{\tau} (P'(t) - P(t))$$

**CERA
Concentration**

**Negative
Feedback**



RET = Reticulocytes
RBC = Red Blood Cell

Mechanism of Epoetin pharmacodynamics

Model equations

$$RBC(t) = RBC(0) + \int_0^t (P(t) - \bar{P}_0) dt - \sum_{i=1}^{t_n} \frac{RBC(t_i) * SAM_i}{VOL}$$

$$(t_n < t, t < SPAN)$$

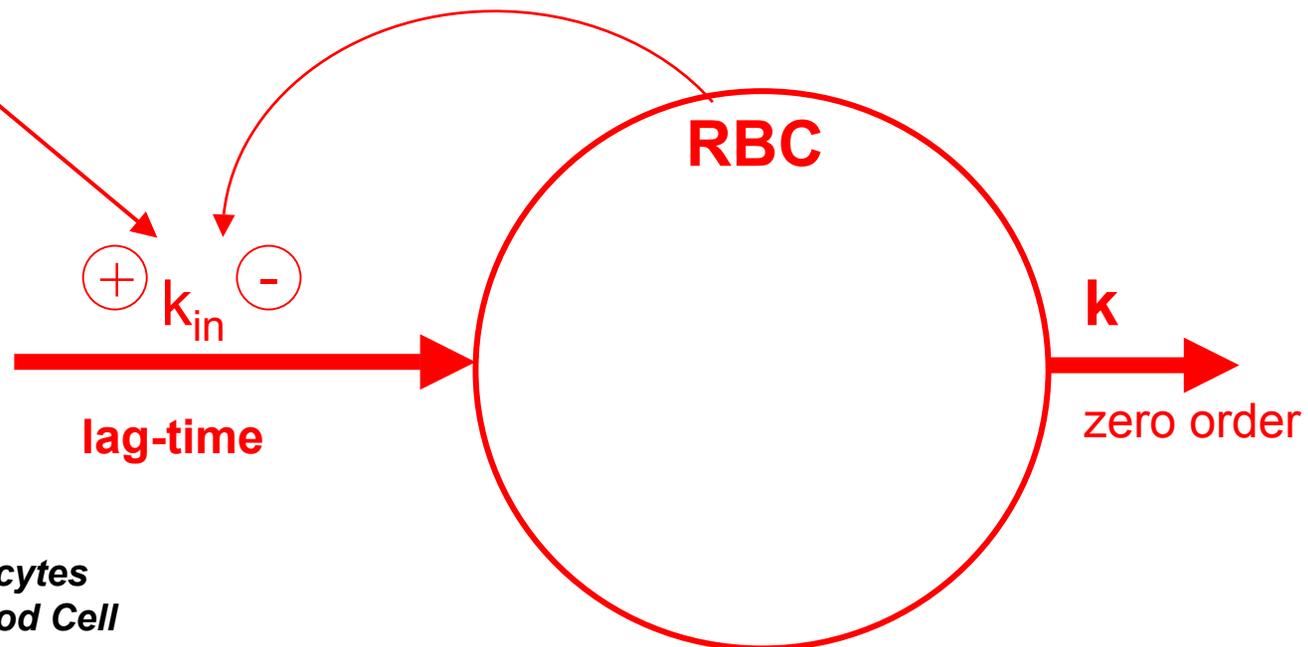
$$VOL = WT / 13$$

$$Hb(t) = RBC(t) * MCH / 1000$$

$$Ht(t) = RBC(t) * MCV / 1000$$

**CERA
Concentration**

**Negative
Feedback**



RET = Reticulocytes
RBC = Red Blood Cell

Mechanism of Epoetin pharmacodynamics

Model equations

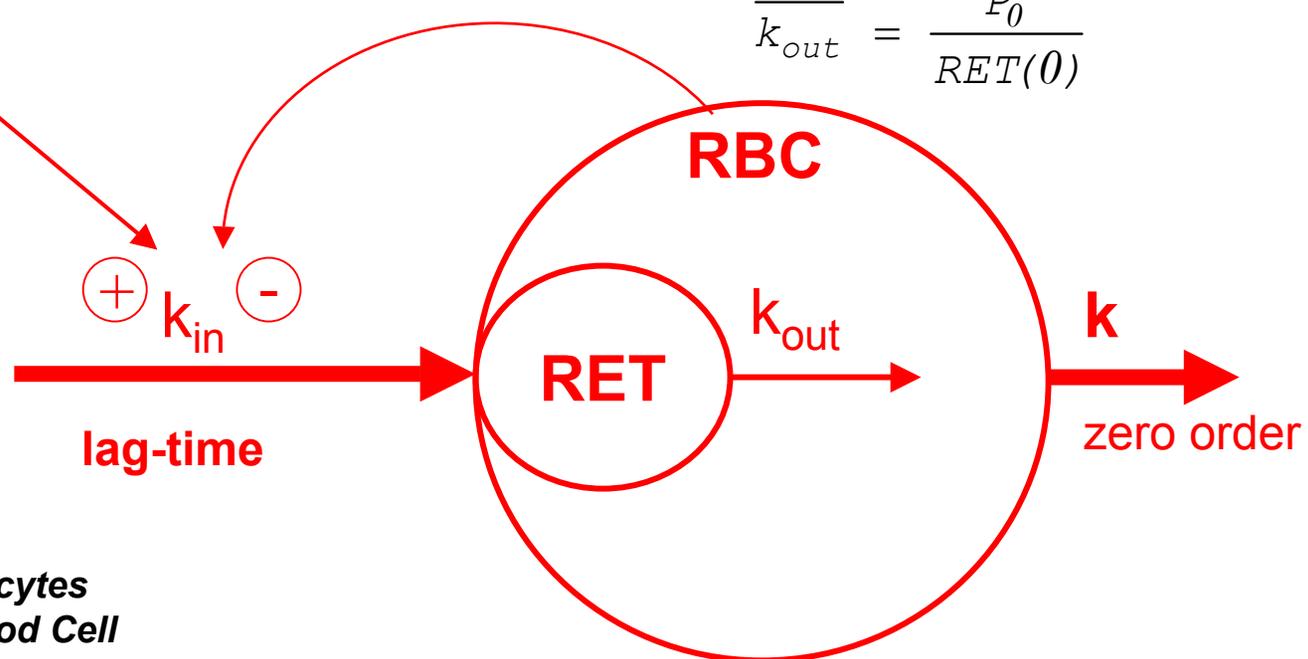
$$\frac{dRET(t)}{dt} = P(t) - RET(t) \times k_{out}$$

$$k_{out} = \overline{k_{out}} \times \left(\frac{\overline{P_0}}{P(t)} \right)^{POW}$$

$$\overline{k_{out}} = \frac{\overline{P_0}}{RET(0)}$$

**CERA
Concentration**

**Negative
Feedback**



RET = Reticulocytes
RBC = Red Blood Cell

PK/PD modeling with healthy volunteers' study

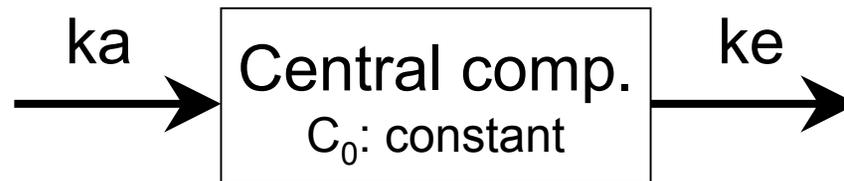
Study design

- Subjects: 46 healthy volunteers
- Dosage of Epoetin beta:
 - 1) 50 IU/kg x3 / week sc
 - 2) 150 IU/kg x1 / week sc
 - 3) 300 IU/kg x1 / 2 weeks sc
- Administration period: 4 weeks
- Variables: RBC, Hb, Ht, reticulocyte & plasma erythropoietin concentrations

PK/PD modeling with healthy volunteers' study

PK analysis

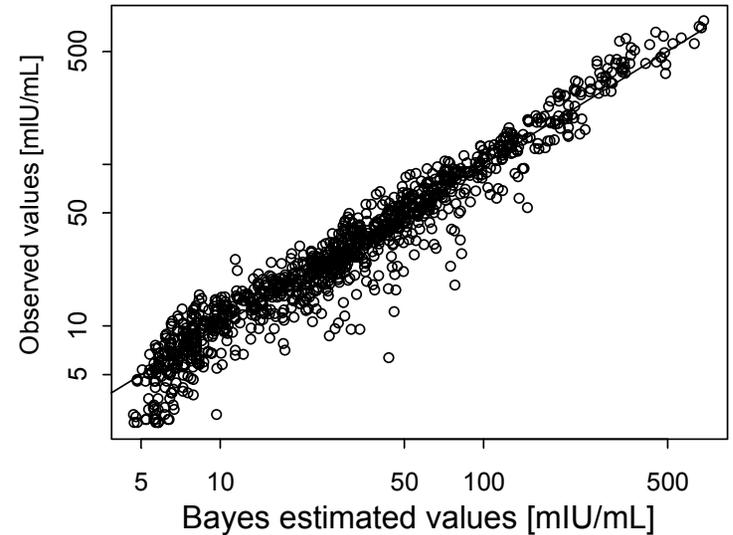
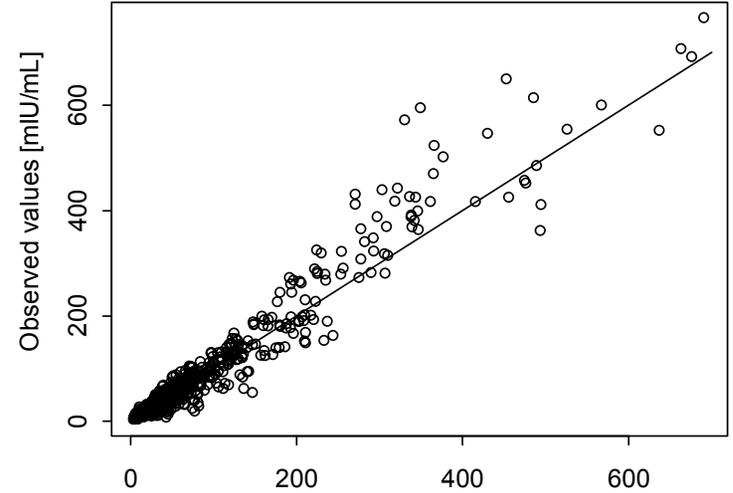
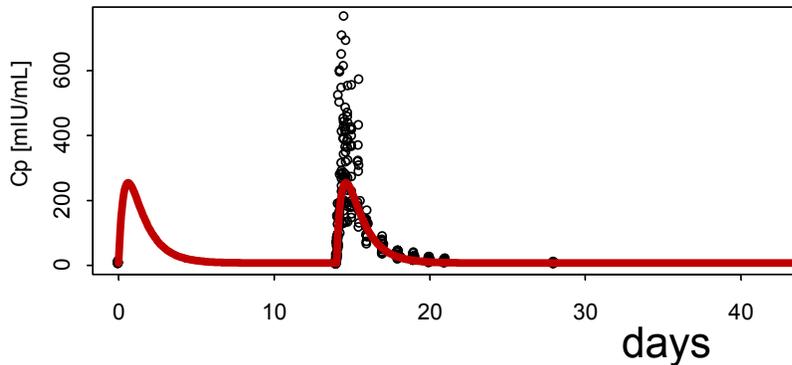
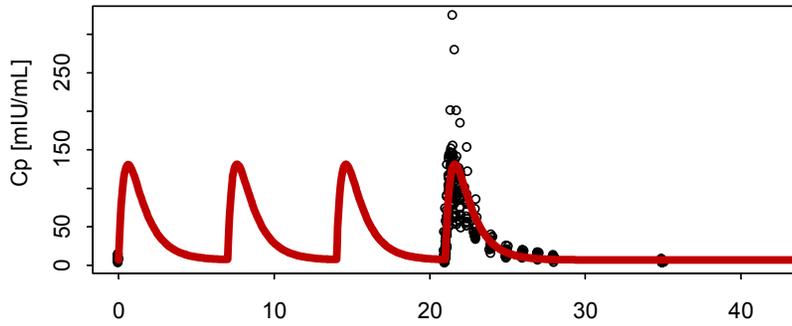
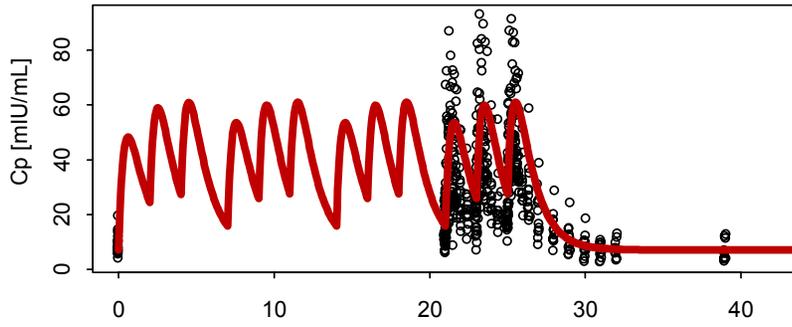
- The PK analysis was performed using a one compartment, first order absorption, first order elimination model including an endogenous level



- The following PK/PD analysis considered the Bayes estimated PK parameters of each subject

PK/PD modeling with healthy volunteers' study

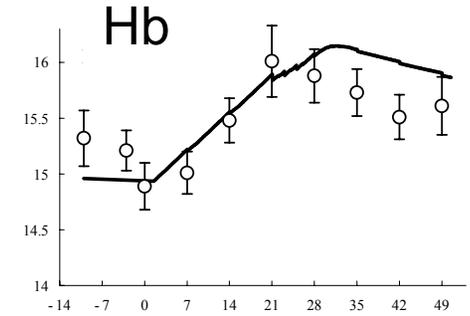
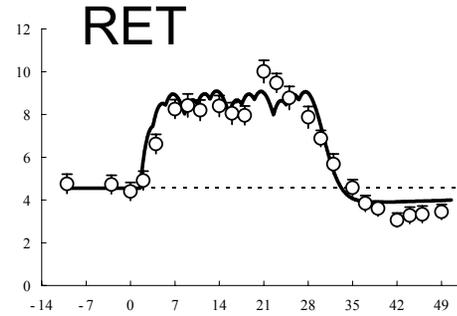
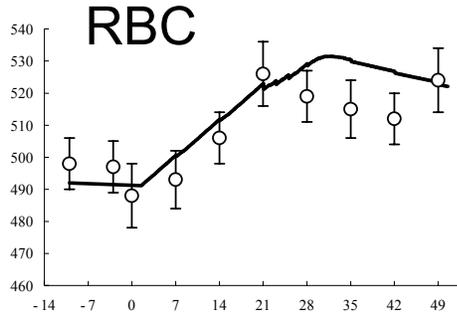
PK analysis with a simple model was enough for the following PK/PD analysis



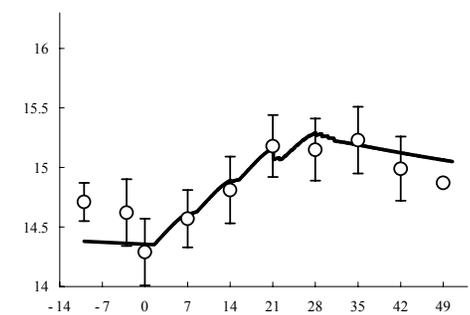
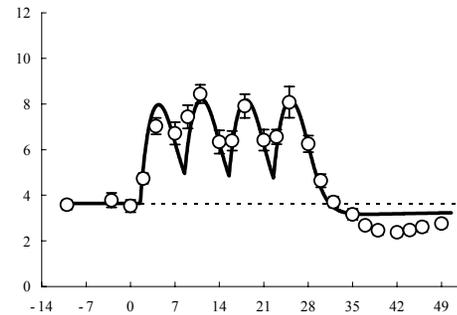
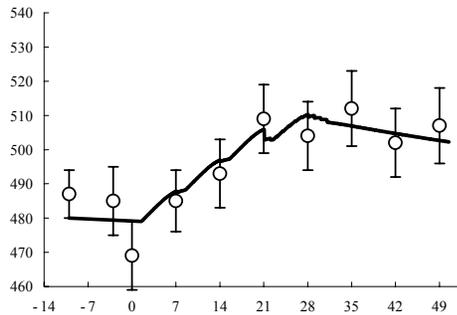
PK/PD modeling with healthy volunteers' study

Hematological responses for each cohort

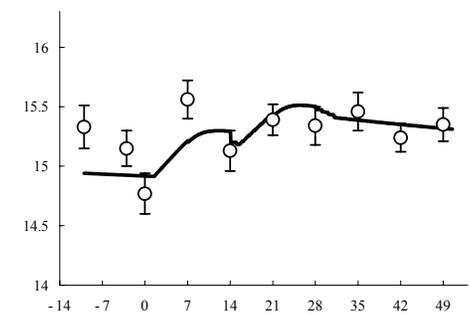
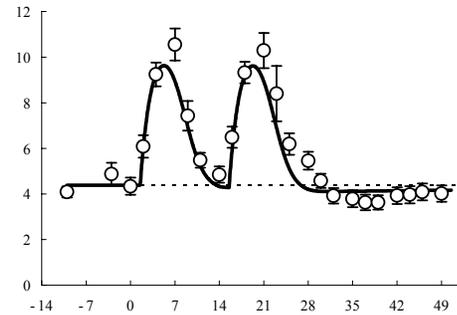
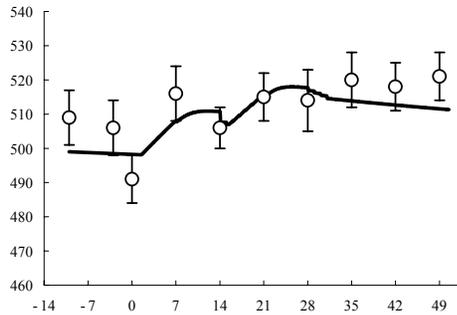
50 IU/kg



150 IU/kg



300 IU/kg



mean±SE

PK/PD modeling with healthy volunteers' study

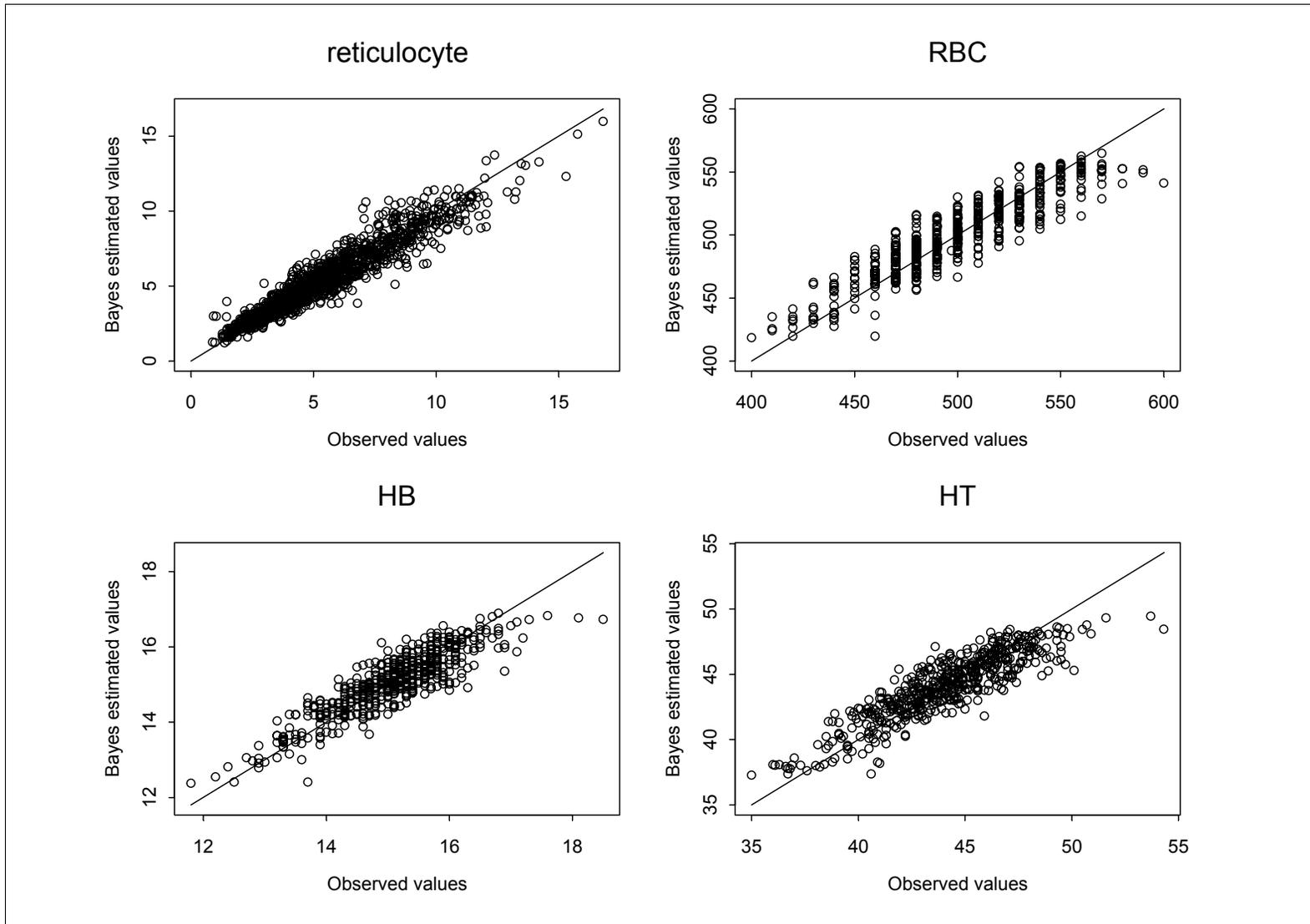
The values of PK/PD parameters were reasonable



	Theta	Eta	
EMAX (x10 ⁴ /uL/day)	4.74	1.292E-06	CV(%)
EC50 (mIU/mL)	25.2	101.5	CV(%)
SLOPE (dL/g)	0.274	77.8	CV(%)
POW	1.05	-	
transit time (day)	4.76	22.2	CV(%)
MCH (pg)	30.1	1.077	SD
MCV (uL)	88.2	2.81	SD
RBC0 (x10 ⁴ /uL/day)	492	28.6	SD
RET0 (x10 ⁴ /uL/day)	4.15	27.2	CV(%)
		SIGMA	
RET (x10 ⁴ /uL/day)		14.9	CV(%)
RBC (x10 ⁴ /uL/day)		15.8	SD
Hb (g/dL)		0.458	SD
Ht (%)		1.46	SD

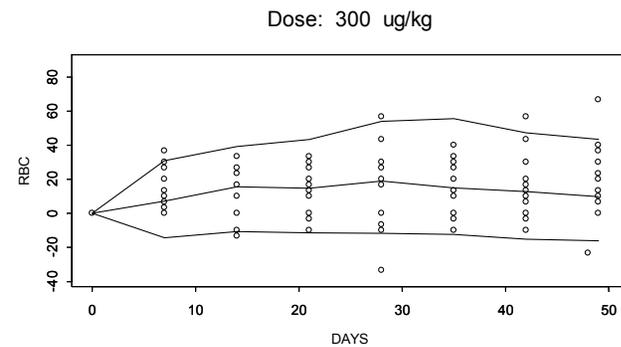
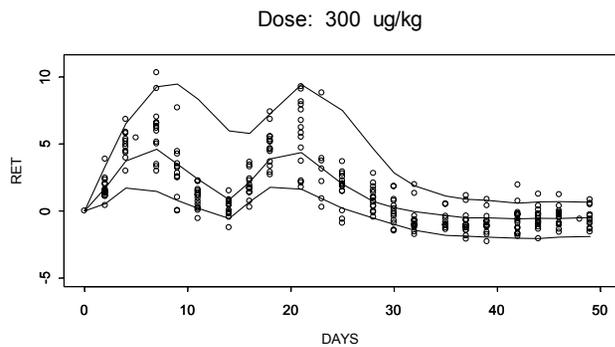
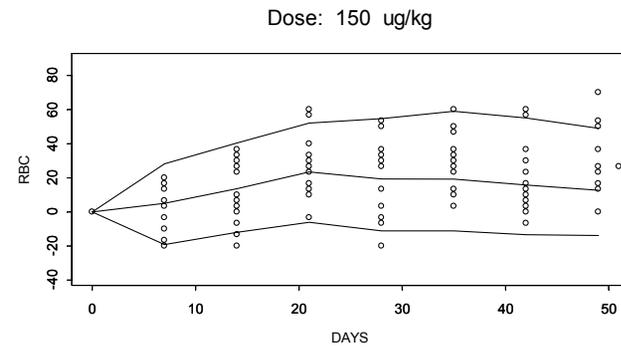
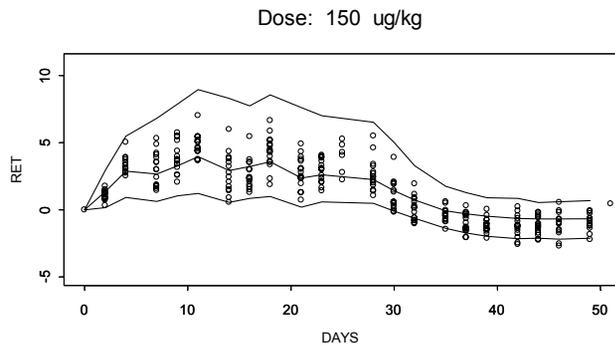
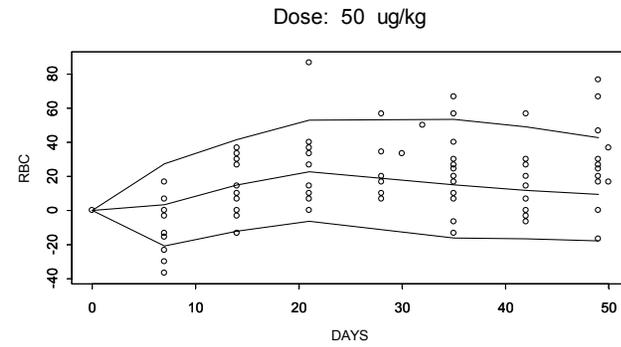
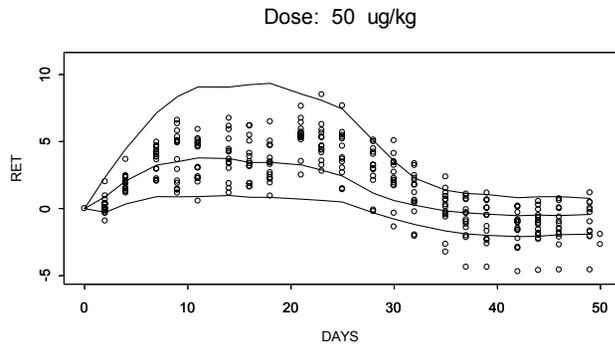
PK/PD modeling with healthy volunteers' study

Bayes estimated values showed a high correlation with the observed values



PK/PD modeling with healthy volunteers' study

Simulated values distribution matches the ones of observed values (PPC)



Reticulocyte

RBC

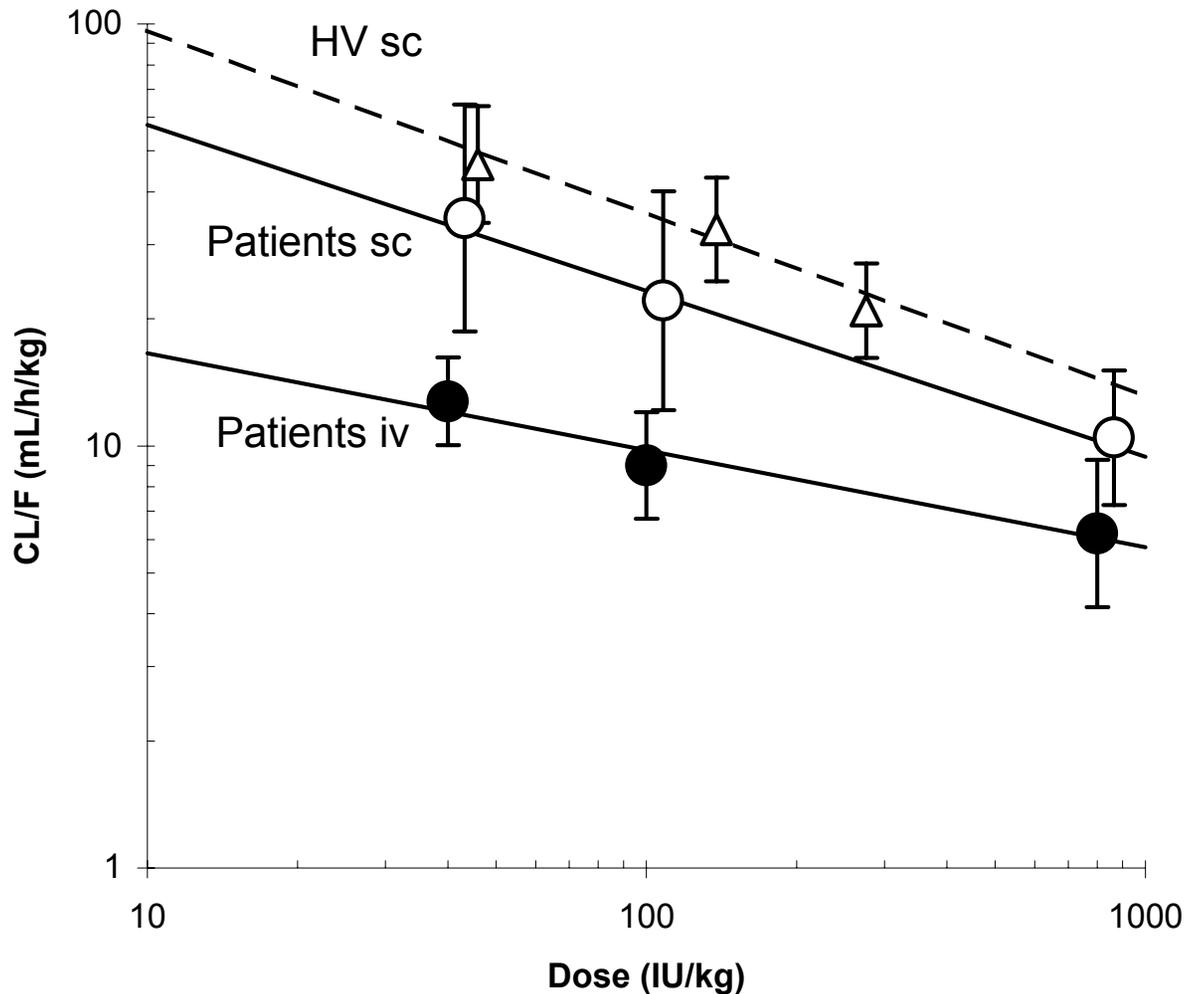
Simulation for renal anemia patients' studies

Simulation method

- Only **RBC baseline** and **clearance** were modified from HV
- The studies for the reference were selected for
 - SC weekly
 - SC daily
 - IV x 3 / week
- Simulation was performed using Trial Simulator TM (n = 10000) for each cohort

Simulation for renal anemia patients' studies

Clearance in renal anemia patients

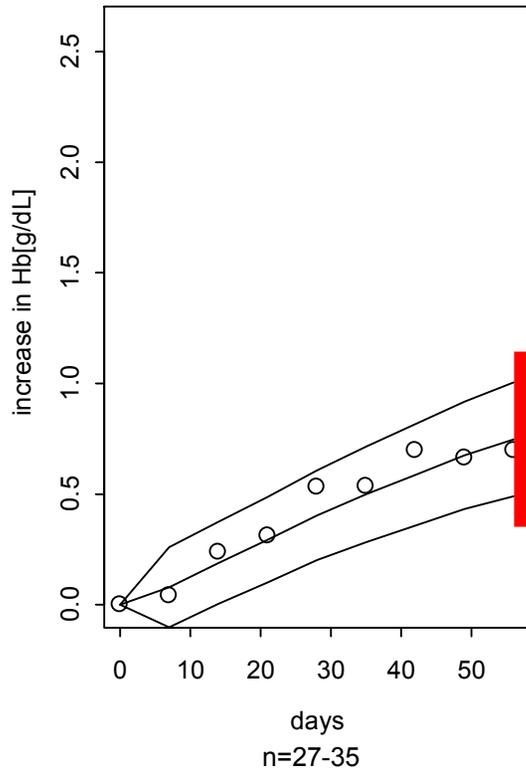


mean±CV

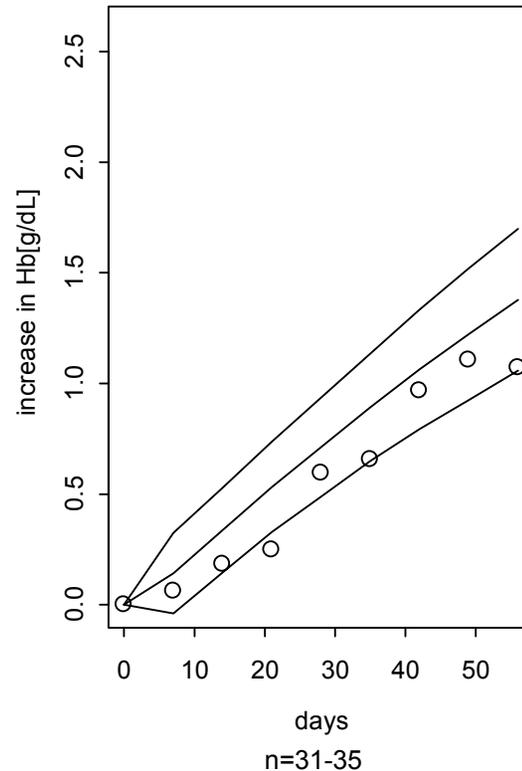
Simulation for renal anemia patients' studies

Study 1: sc weekly, Hb time course was predicted for 8 weeks

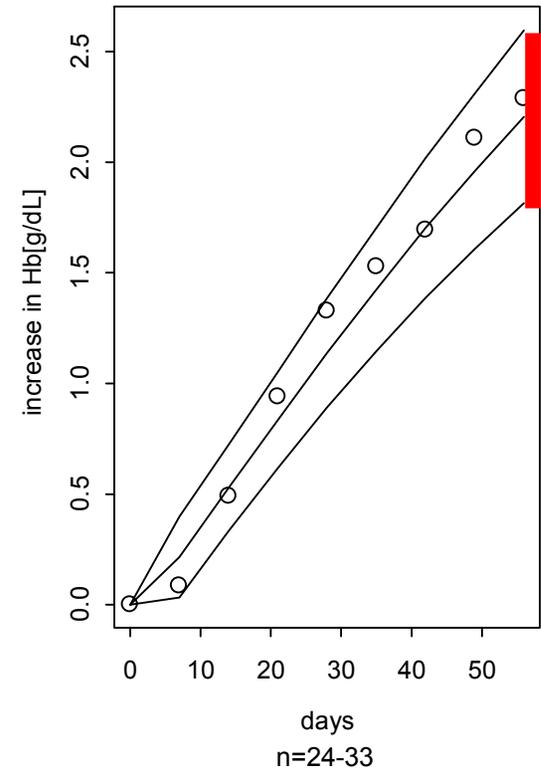
1500IU SC x 1/week



3000IU SC x 1/week



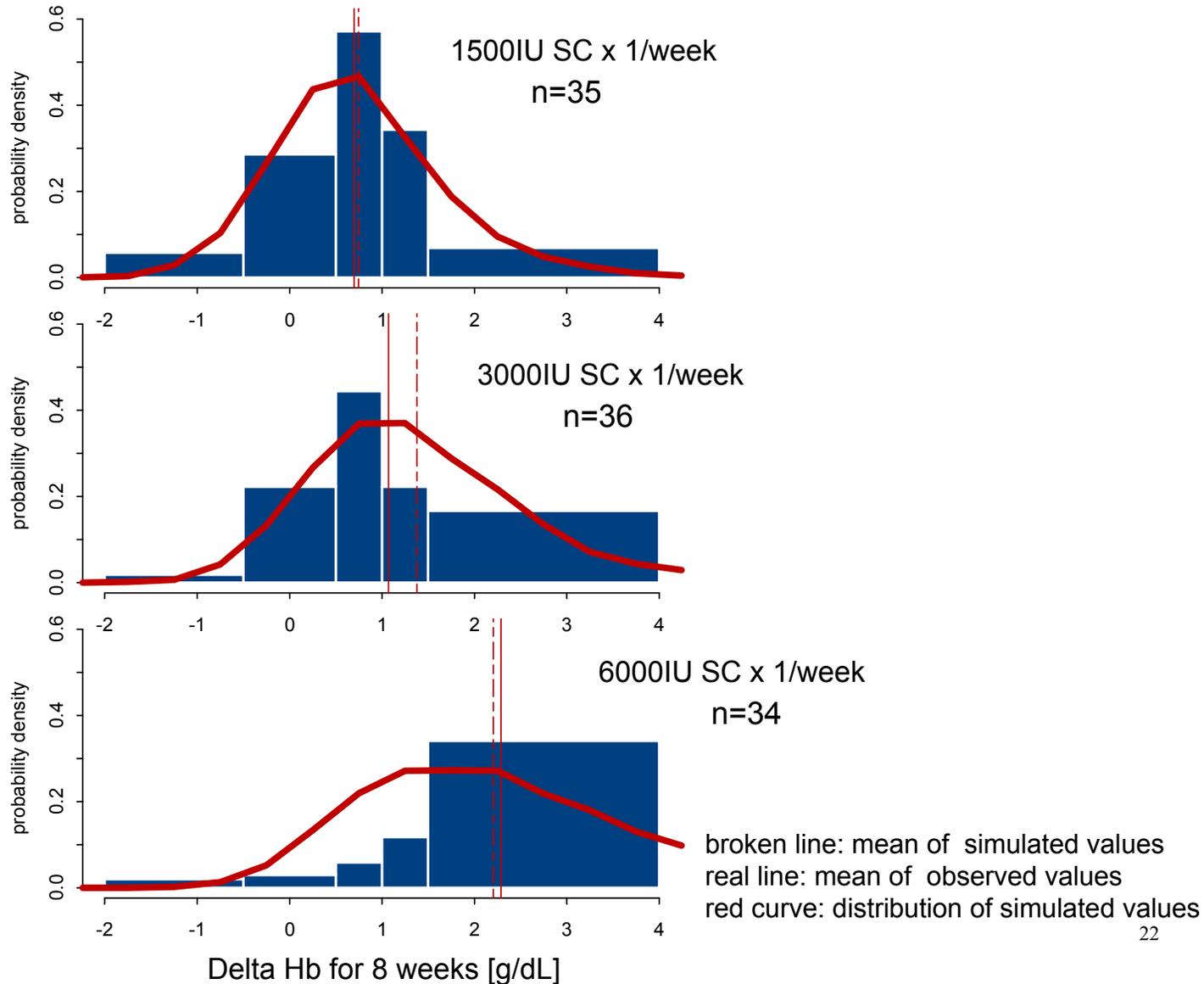
6000IU SC x 1/week



Line: median & 90%CI for simulation
Circle: mean of observed values
Hb₀: 7.7 g/dL

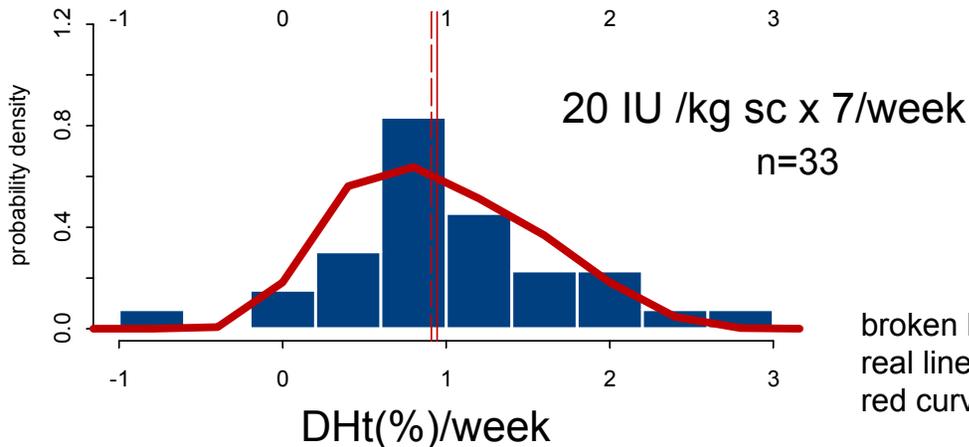
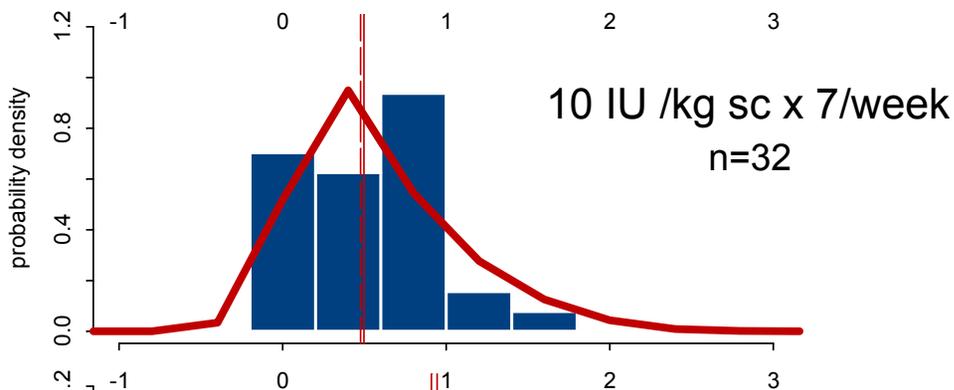
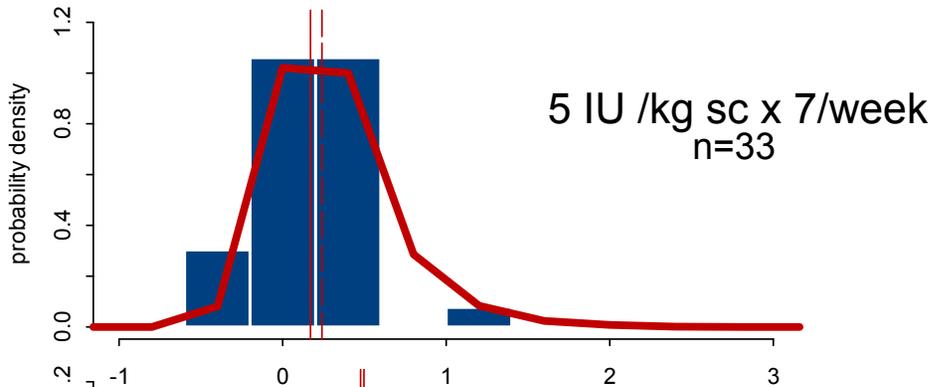
Simulation for renal anemia patients' studies

Study 1: sc weekly, the distribution of ΔHb was predicted



Simulation for renal anemia patients' studies

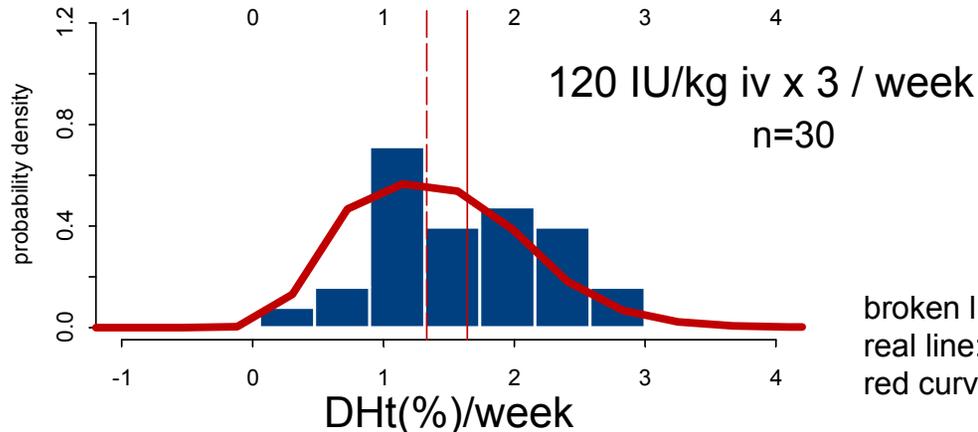
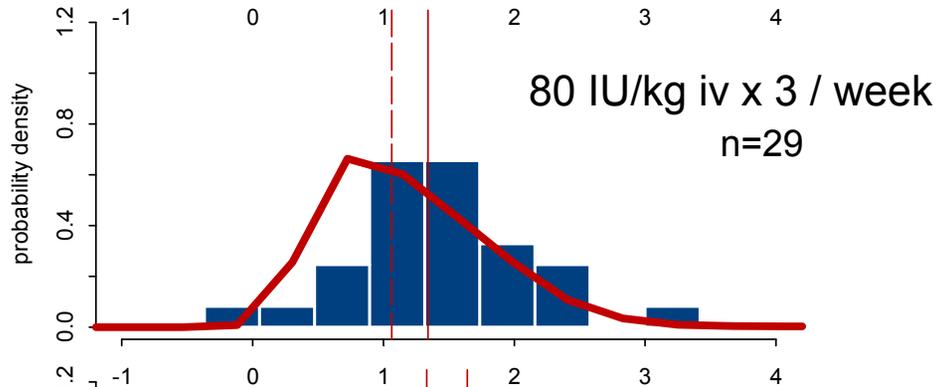
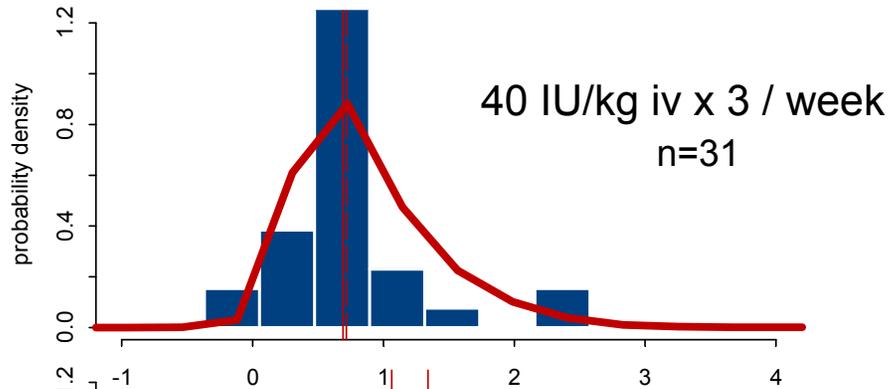
Study 2: sc daily, the distribution of Ht slope was predicted



broken line: median of simulated values
real line: median of observed values
red curve: distribution of simulated values

Simulation for renal anemia patients' studies

Study 3: iv x3 / week, the distribution of Ht slope was predicted

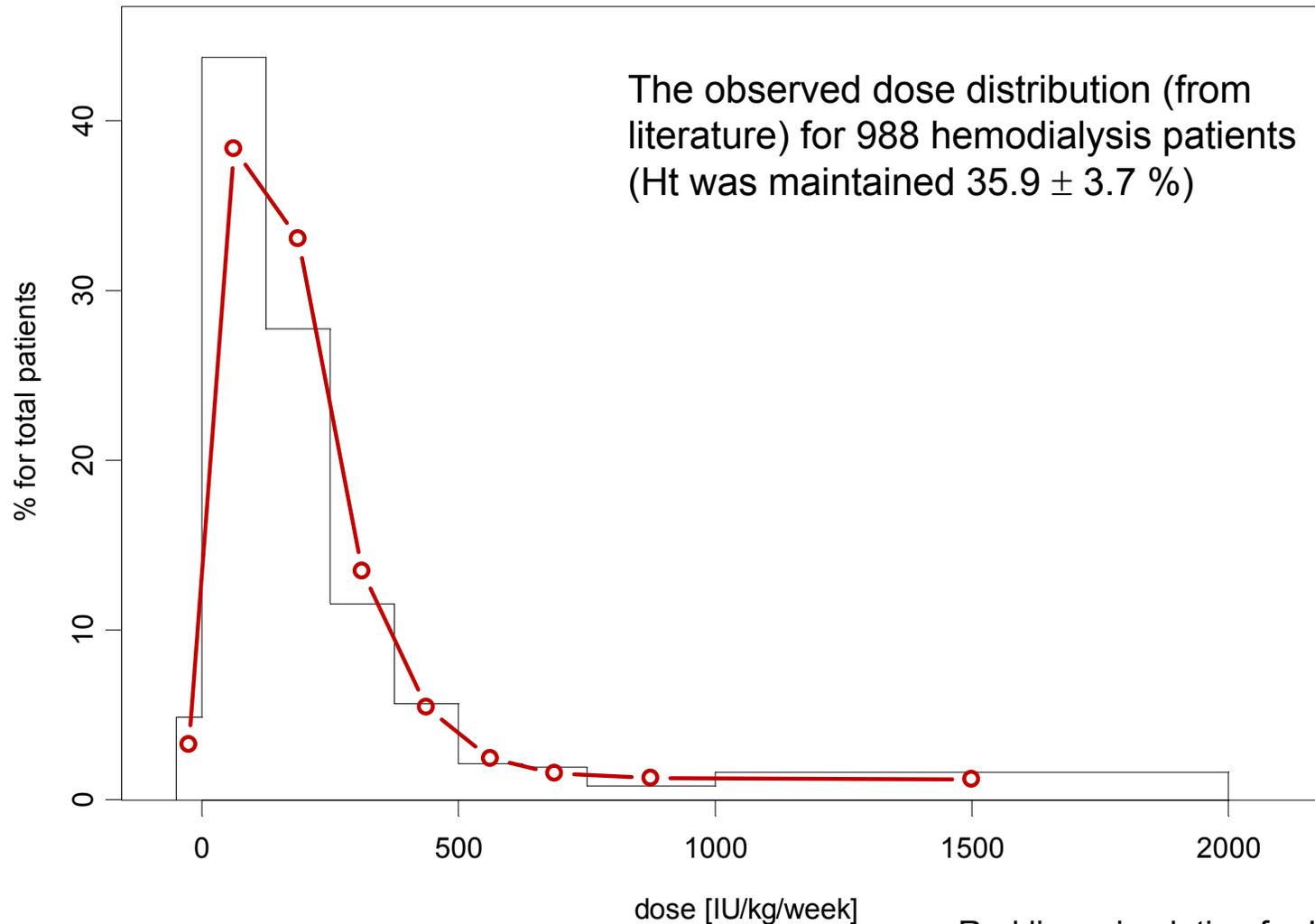


broken line: median of simulated values
real line: median of observed values
red curve: distribution of simulated values

Simulation for renal anemia patients' studies

Maintenance study:

the model could also predict the distribution of maintenance dose



Red line: simulation for IV x3 / week

Conclusions

- A mechanism-based PK/PD model was developed which is able to describe the time courses of hematological responses for Epoetin beta in healthy volunteers
- This model also predicted the time courses in renal anemia patients
- The model predicts not only the mean values but also the individual values' distribution
- The model was useful for predicting responses with different dose routes, different dose frequency
- The model was useful for predicting maintenance dose