

PK Projections for Therapeutic Proteins in Entry Into Human Studies: Roche pRED Experience From 2004 to 2016



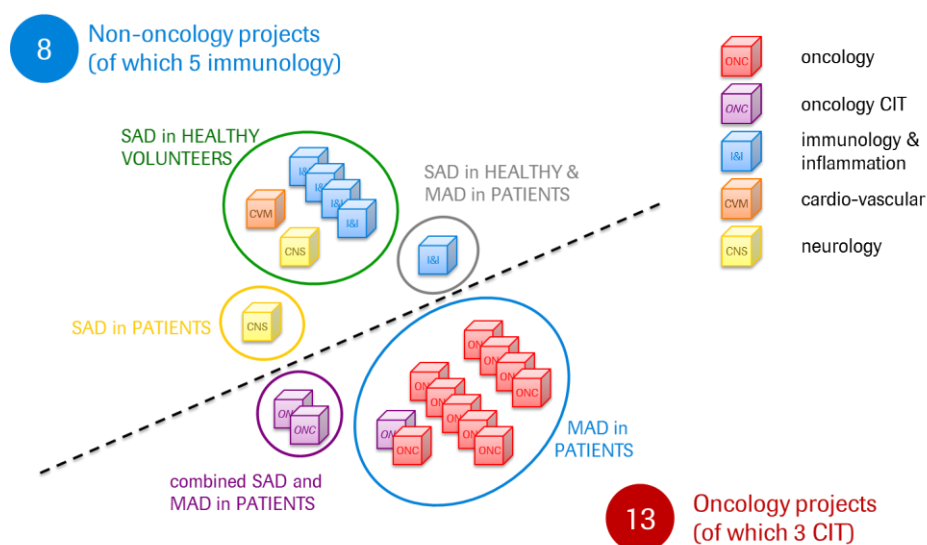
Hans Peter Grimm (1), Siân Lennon-Chrimes (2), Peter N. Morcos (3), Richard Peck (1), Thierry Lavé (1)

Roche Pharmaceutical Research and Early Development, Pharmaceutical Sciences

(1) Roche Innovation Center Basel, Switzerland, (2) Roche Innovation Center Welwyn, UK, (3) Roche Innovation Center New York, USA

1 – Introduction/Objectives

Defining safe and pharmacologically meaningful doses for clinical studies at Entry Into Human (EIH) strongly relies on human PK projections. These are based on pre-clinical PK and other information for the molecule and to some extent inference from similar molecules. Here, we present the results of a review of the methodology and the success of model-based prediction of exposures for EIH studies with therapeutic proteins in Roche pRED (Pharma Research Early Development) between 2004 and 2016. The therapy areas represented in this group of molecules and the study designs employed are shown below.



2 – Methods

Information on models for human PK prediction was systematically collected for all 21 Roche pRED-sponsored monotherapy projects with therapeutic proteins achieving EIH between 2004 and 2016. Where a prediction model was available prior to EIH, its quality was assessed based on C_{max} and AUC. For this, the reported models were implemented in Berkeley-Madonna and simulations run reflecting the design of the clinical studies. Predictions were considered adequate when they were within 2-fold of the averaged observed values (NCA) for >90% of the size-weighted cohorts. Where several prediction scenarios were used in parallel, the model predicting the higher exposure was used for comparison with observations.

3 – Background on Prediction Methodology

PK prediction was generally performed by allometry based on PK in cynomolgus monkeys. This approach is consistent with that described in recent publications [1-6].

PK Model. Linear 2-compartment models are usually the backbone of PK models fitted to the PK from cynomolgus monkey and scaled to human. TMDD is then often captured by a concentration-dependent clearance ($V_{max}-K_M$).

$$\begin{aligned} V_{cen} \cdot C_{cen}' &= -Q \cdot (C_{cen} - C_{per}) - CL \cdot C_{cen} - \frac{V_{max} \cdot C_{cen}}{K_M + C_{cen}} \\ V_{per} \cdot C_{per}' &= Q \cdot (C_{cen} - C_{per}) \end{aligned}$$

Allometry. Simple body-weight proportionality is assumed for volumes. Clearances are scaled with an exponent b . Where TMDD is modeled as $V_{max}-K_M$ -model, K_M is assumed invariant between species while V_{max}/K_M is scaled as a clearance.

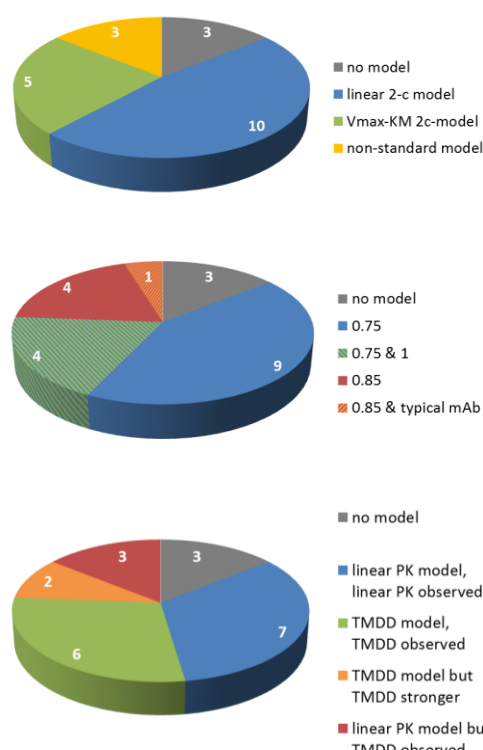
$$\begin{aligned} CL_{hu} &= CL_{cy} \cdot \left(\frac{BW_{hu}}{BW_{cy}}\right)^b \quad \text{and} \quad Q_{hu} = Q_{cy} \cdot \left(\frac{BW_{hu}}{BW_{cy}}\right)^b \\ K_{M,hu} &= K_{M,cy} \quad \text{and} \quad \frac{V_{max,hu}}{K_{M,hu}} = \frac{V_{max,cy}}{K_{M,cy}} \cdot \left(\frac{BW_{hu}}{BW_{cy}}\right)^b \end{aligned}$$

4.1 – Results: Prediction Methodology Applied

Model Type. Models for human PK prediction were available in 18 of the 21 projects investigated. 10 of the 18 models were linear 2-compartment models. Another 5 models captured the impact of TMDD by a scaled $V_{max}-K_M$ model. In the remaining cases more complex models were used.

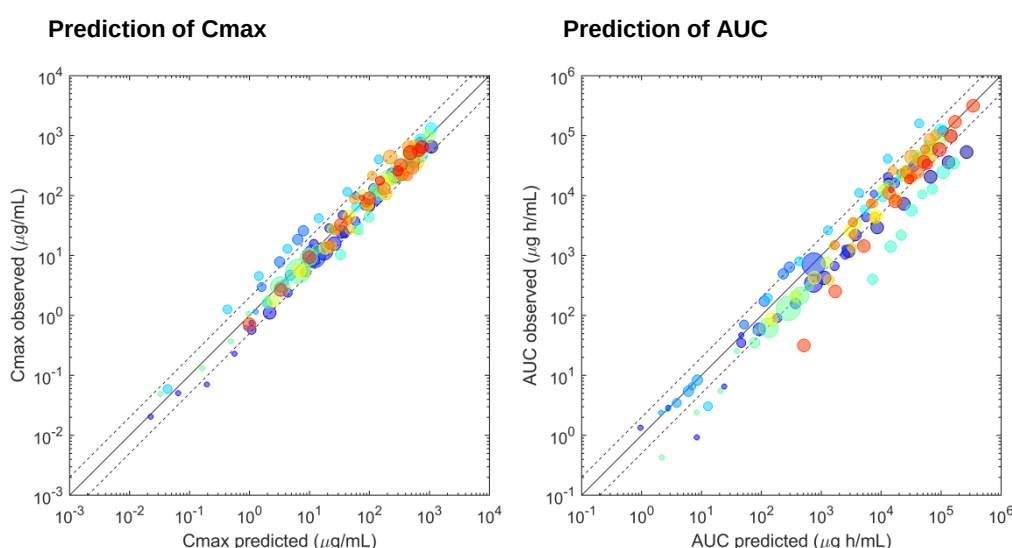
Allometry. Models were built on PK from cynomolgus monkeys and allometrically scaled using fixed exponents. Exponents for clearance have evolved over time from 0.75 to 0.85. In several cases two parallel prediction scenarios were used to bracket the prediction; this included one case in which the PK of a typical monoclonal antibody was used.

TMDD. Linear PK was observed in human in 7 of 10 cases where a linear model was used. TMDD was confirmed in human in all 8 cases where it was predicted. In 3 cases, TMDD was observed where a linear model was used; in 2 other cases TMDD was seen to be significantly stronger than predicted by the model. Cynomolgus monkey was cross-reactive in all cases where TMDD was observed in human.



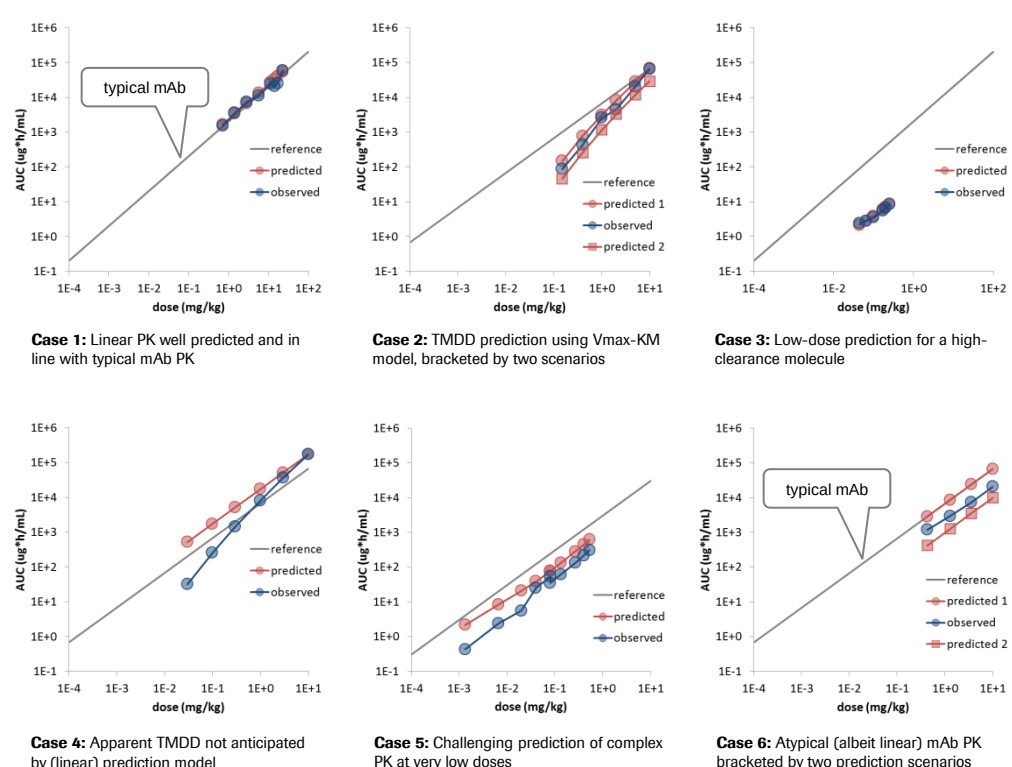
4.2 – Results: Overall Quality of Prediction

More than 80% of the predictions of C_{max} and roughly 55% of predictions of AUC were found within 2-fold of observations. In seven of the 10 cases where a linear model was used this was found to be adequate.



- Each compound represented by one color
- Each cohort represented by one bubble, size corresponding to cohort size
- When more than one prediction was available, the more conservative prediction was used

4.3 – Results: Case Examples of Human PK Prediction



5 – Conclusions

This systematic review of model predictions for human PK predictions for therapeutic proteins shows that the relatively simple allometric scaling from the PK in non-human primates provides useful and robust projections for the planning of EIH studies. Challenges, where they appeared, were most often related to the TMDD and its projection, exacerbated by the very low doses used in some studies with compounds for cancer immunotherapy. This underlines the need in developing robust methods to improve confidence in mechanistic and/or physiologically based models for human PK prediction.

6 – Acknowledgments

This review relies on the work and dedication of a large number of scientists from various disciplines acknowledged here: Translational M&S, DMPK, LM Bioanalytical Sciences, Clinical Pharmacology, Large Molecule Research, and many more.

6 – References

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