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Sunrise Session:
Target-Mediated Drug Disposition: Opportunities, Practical Challenges and Pitfalls

TMDD Model and its Application in the Early Clinical Development of Antibody Therapeutics

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Introduction

- Questions that this talk aims to highlight:
  - Main features of the TMDD model and its approximations;
  - How modeling can be used at each stage of drug development;
  - Why it is even more important to use modeling in drug development of biologic compounds;
  - Some experience-based recommendations for drug development of mAb,
- Mostly based on our experience and publications, but other useful ideas that we found in the literature will also be presented.
- Talk will concentrate on early phases (pre-clinical to end of Phase 2).

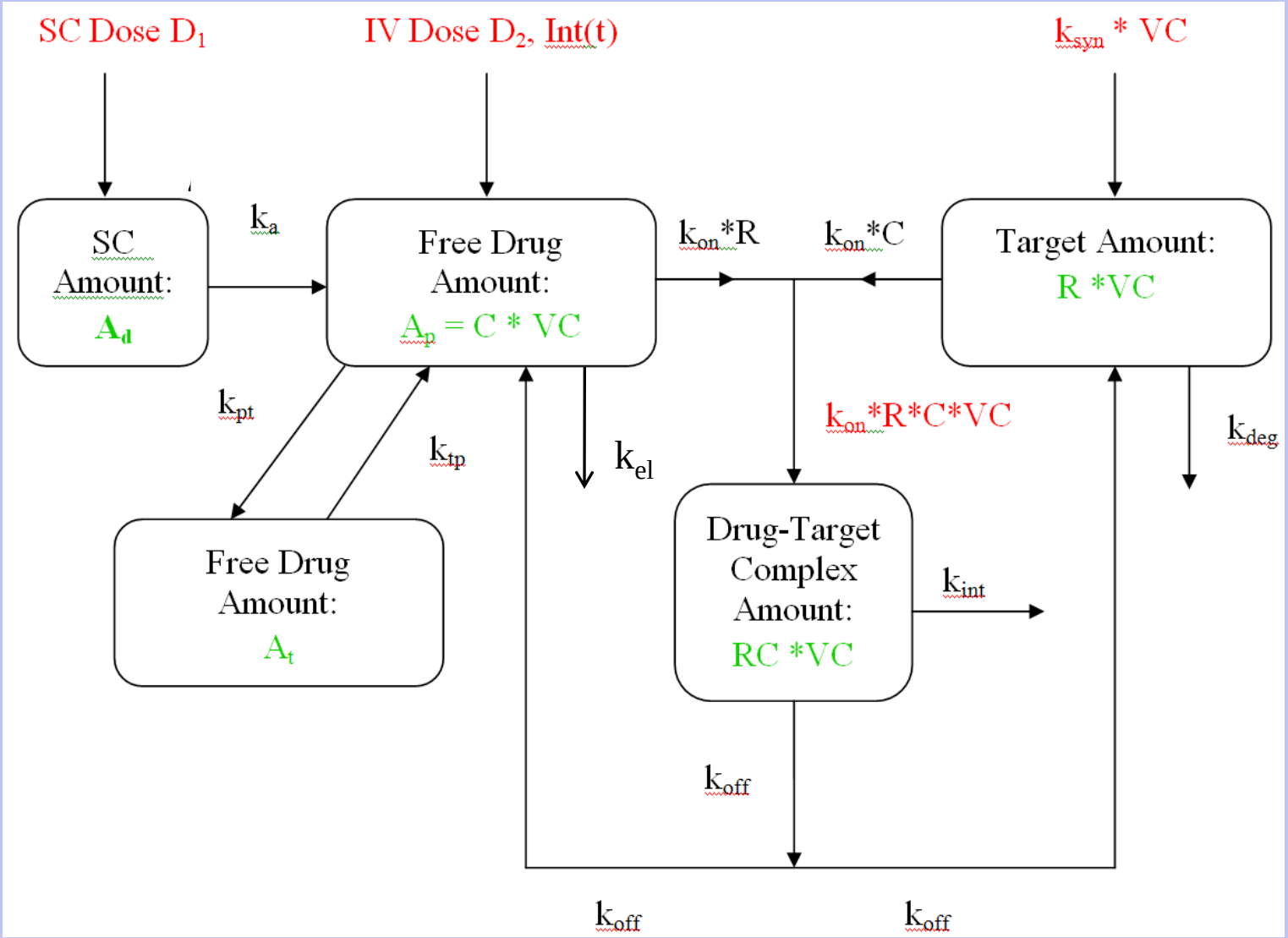
TMDD model

Gerhard Levy, Clinical Pharmacology & Therapeutics (1994) 56:248-252.
Don Mager and Bill Jusko, *JPP* (2001) 28: 507-532.

Red:
input

Green:
amount

Black:
rate
constants



Approximations of the TMDD model

Quasi-Equilibrium (Rapid Binding; QE): $\frac{C \cdot R}{RC} = K_D$

Mager and Krzyzanski [*Pharm Res* (2005) 22(10): 1589-1596]

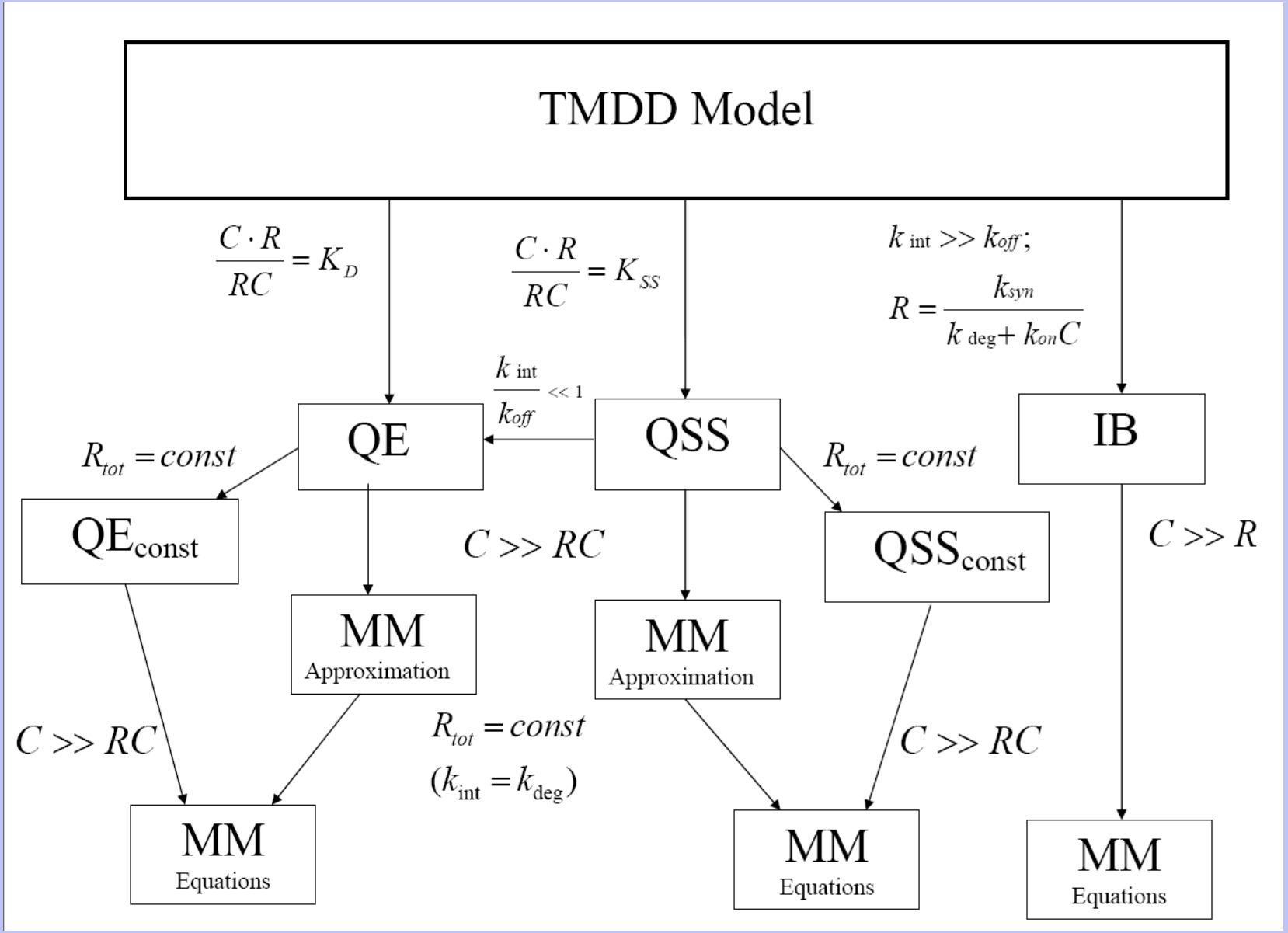
Quasi-Steady-State (QSS): $\frac{C \cdot R}{RC} = K_{SS}$

Gibiansky, Gibiansky, Kakkar, Ma [*JPP* (2008) 35(5):573-91]

Irreversible binding (IB): $k_{\text{int}} >> k_{off}; \quad R = \frac{k_{syn}}{k_{\text{deg}} + k_{on} C}$

Gibiansky, Gibiansky [PAGE 2010, abstract 1728]

Hierarchy of TMDD Approximations



How to select correct approximation?

Approach 1

Move from the bottom to the top, based on the model fit:

- Start with the linear model;
- Apply linear model with parallel linear and Michaelis-Menten elimination;
- Apply QSS approximation;
- Increase the complexity while checking the model fit and relative standard errors of the parameter estimates;

Approach 2

Select approximation based on biology (properties of the drug and the target):

- Soluble or membrane target?
- Rapid or slow elimination of the drug-target complex?

Target type: Soluble versus Membrane

What to expect for soluble low-molecular-weight target

- Likely accumulation of the drug-target complex;
- Free and/or total drug concentration is available;
- Total target or drug-target complex concentration is often available;
- The QSS approximation is the expected model.

What to expect for membrane target with fast target turn-over

- Total target concentration is likely to be small;
- Only free drug concentration is available;
- Target measurements are rarely available;
- The MM approximation (or equations) is the expected model

Each rule has exceptions !!!

Modeling of drugs with TMDD

- TMDD equations provide useful framework to describe drug and target concentrations for biologics;
- TMDD equations are based on many implicit and explicit assumptions; validity of these assumption should be evaluated on a case by case basis;
- Full TMDD model is rarely identifiable given the clinical data; appropriate approximations can (or even should) be used;
- TMDD model approximations provide robust, identifiable models that describe all TMDD features;
- Selection of the most suitable approximation should be guided by biological considerations and confirmed by the model diagnostics;
- Parameters of approximations can be expressed in terms of mechanistic parameters of the TMDD system;
- Use of incorrect approximations may result in biased parameter estimates.

TMDD and design of first-in-human (FIH) trials

Prediction of exposure from animals to humans:

- Small molecules:
  - Allometric scaling with several relevant species
  - Often: $CL \sim WT^{0.75}$; $V \sim WT$
- Biologics:
  - Allometric scaling ?
  - $CL \sim WT^{\alpha}$; $V \sim WT$; How to scale non-linear parameters?

Allometric Scaling of Therapeutic Proteins

W. Wang, T. Prueksaritanont. Prediction of Human Clearance of Therapeutic Proteins: Simple Allometric Scaling Method Revisited. Biopharm. Drug Dispos. 31: 253–263 (2010)

J. Ling, et al. Interspecies Scaling of Therapeutic Monoclonal Antibodies: Initial Look. J Clinical Pharmacology 2009;49:1382-1402

J. Dong, et al. Quantitative Prediction of Human Pharmacokinetics for Monoclonal Antibodies. Clin Pharmacokinet 2011; 50 (2): 131-142

R. Deng, et al. Projecting human pharmacokinetics of therapeutic antibodies from nonclinical data: what have we learned?.MAbs. 2011 Jan-Feb;3(1):61-6

- Evaluation of biologic compounds including mAbs and fusion proteins indicated that allometric scaling with power 1 for volume and 0.75-1 (optimal 0.8-0.9) for clearance provides good estimates of the model parameters that describe volumes and non-specific clearance.
- Simple allometric scaling (without detailed investigation of the target properties) may provide incorrect predictions of the concentration-time profiles at low doses and concentrations.

How to Scale Target Parameters?

- Binding parameters can be measured in-vitro (k_{on}, k_{off}, $K_D=k_{off}/k_{on}$);
- Baseline target concentration can be measured and used to estimate the expected range of target parameters (k_{syn}= Base k_{deg});
- Target turn-over is very important: target-mediated elimination is proportional to the target production rate k_{syn};
- Some targets have consistent turnover across species. If target expression levels and kinetics differ between species, it is essential to have good measurements in humans;
- Predictions for human mAbs should be based on kinetics of human target turnover;
- Some examples were provided in [1];
- Expected receptor occupancy is an important characteristics in selection of the starting dose;

[1] Lowe PJ, Tannenbaum S, Wu K, Lloyd P, Sims J., On setting the first dose in man: quantitating biotherapeutic drug-target binding through pharmacokinetic and pharmacodynamic models. Basic Clin Pharmacol Toxicol. 2010 Mar;106(3):195-209

Literature Example

[1] KT Luu , S Bergqvist, E Chen, D Hu-Lowe, E Kraynov, A Model-Based Approach to Predicting the Human Pharmacokinetics of a Monoclonal Antibody Exhibiting Target-Mediated Drug Disposition, JPET 03/13/2012, DOI:10.1124/jpet.112.191999

- Problem: Predict PK of an IgG2 antibody directed against human ALK1 receptor;
- Data:
  - Cyno monkeys PK data;
  - Human and monkey binding parameters k_{on}, k_{off} ;
  - Human and monkey internalization rate k_{int};
  - Human k_{deg}; for monkeys, assume to have the same value.
- Monkey PK model:
  - Full TMDD model with binding in the central compartment;
  - Parameters k_{int}, k_{deg}, k_{on}, and k_{off}, were fixed;
  - Parameters k_{el}, k_{tp}, k_{pt}, $R_0=k_{syn}/k_{deg}$, and V_c were estimated from the data.

Literature Example

- Human data simulation assumptions:
  - Allometric scaling of k_{el}, k_{tp}, and k_{pt} with the WT power of -0.25 ;
  - V_c fixed to the plasma volume (corresponds to WT scaling with power 1.15);
  - $R_0=k_{syn}/k_{deg}$ was assumed to be the same as in monkeys (from the model fit);
  - Inter-subject variability of 20% for k_{el}, k_{tp}, k_{pt}, R_0, and $V_{c.}$
- Results: for a wide range of doses (0.5 to 4.5 mg/kg),
  - AUC, C_{max}, CL: 20-60% difference relative to the observed NCA values;
  - $t_{1/2}$, V_c: under predicted by about 20-70%, especially for the lower doses.
- **Comment**: it was unusual that human V_c was fixed to the plasma volume while monkey V_c was estimated (~60% of monkey plasma volume). Should the authors use allometric scaling for V_c with power 1, prediction of the human V_c would be about 40% lower, and PK predictions would not be as good. No explanation or discussion was provided.

FIH: fixed versus weight-proportional dose

D. Wang et al. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49:1012-1024

S. Zhang. Fixed Dosing Versus Body Size-Based Dosing of Therapeutic Peptides and Proteins in Adults. J Clin Pharmacol. 2011. DOI: 10.1177/0091270010388648S.

- Analysis of mAbs, peptides, and proteins literature models
  - Looked at fixed versus body-size dosing in decreasing IIV of AUC and C_{max}
  - Results suggested similar performance
  - Authors recommended fixed dosing for FIH, and modeling later

Opinion:

- Examples with no weight-dependence of clearance and volume are not very convincing (possibly, insufficient data rather than no dependence);
- The idea of fixed FIH dosing is reasonable;
- These works provide arguments to use fixed-dose regimen in FIH studies.

Similar aguments/conclusions: S Bai et al. A Guide to Rational Dosing of Monoclonal Antibodies Clin Pharmacokinet 2012; 51 (2): 119-135

Summary

- Model-based design of the FIH studies is even more important for biologics than for small-molecules drugs since simple rules do not work for biologics.
- Volume and non-specific clearance parameters of the TMDD model can be successfully predicted based on allometric scaling.
- Target-related parameters cannot be scaled from the animal data. Careful examination of the human biology versus animal model biology in combination with available in-vitro data should be used to predict target-related parameters of the TMDD model.
- FIH trial can be conducted with fixed or per-kilogram dose. Model-based analysis should be used to design the dosing regimens for the following trials.

Study Design: Dosing and Sampling Schemes

- Biologics with TMDD:
  - Terminal half-life depends on dose and concentration level;
  - Clearance depends on dose and concentration level;
  - **Intuition and NCA-based rules developed for small-molecule linear drugs may not be applicable to the drug development of biologics**.

Optimal Sampling Schemes

- Important points to consider:
  - Data following administration of wide range of doses are needed to estimate all model parameters;
  - Data immediately following IV administration may not be useful since they cannot be described by the TMDD approximations; some time is needed to equilibrate drug-target binding processes;
  - For mAbs, frequent Day 1 sampling may not be optimal since both clearance and inter-compartment clearance are expected to be low;
  - Frequent sampling could be helpful at the end of the dosing interval, in the concentration range where target-mediated clearance plays a significant role;
  - For soluble targets, measurements of the total drug, drug-target complex and free target (rarely available) concentrations in addition to the free drug levels, can greatly increase precision of the model parameter estimates.

Application of Optimal Design Ideas

Problem: Common sampling schemes used for linear drugs may not be the best for drugs with TMDD.

Possible solution: Optimal design software could be helpful in selection of the optimal sampling scheme. One can use this software to evaluate identifiability of TMDD model parameters and to select the optimal sampling scheme.

Procedure (design evaluation mode):

- Select structural model, model parameters, variability of the model parameters, and residual variability;
- Select number of subjects and sampling schedule;
- Use the optimal design software to compute the expected precision of parameter estimates.

SC Absorption: how to define bioavailability?

- Definition of bioavailability based on the linear kinetics is misleading.
- Bioavailability F_{SC} defined as a ratio of dose-normalized AUCs strongly depends on the IV and SC dose selection [1]
- Bioavailability F_{SC} defined as a ratio of doses that provides equal AUCs is a better measure [2]
- Model-based analysis of IV and SC data is the best way to determine bioavailability.

[1] W Limothai, B Meibohm, Effect of Dose on the Apparent Bioavailability of Therapeutic Proteins that Undergo Target-Mediated Drug Disposition, AAPS 2011 poster

[2] L Gibiansky, E Gibiansky, NBC 2012 poster W3097, May 23, 8 am - 2 pm Nautilus Exhibit Hall

When and how modeling can help: Preclinical

- **Preclinical**
  - **Case 1:** use mouse and monkey data to predict human exposure.
  - **Result:** model predictions based on combined data were unrealistic (did not correspond to the PK parameters of known mAbs). Mouse data were disregarded; monkey data with several fixed allometrtic scaling rules were used to predict the possible range of human exposure.

  - **Case 2:** use monkey data to predict human exposure.
  - **Result:** Monkey data with several fixed allometrtic scaling rules were used to predict the possible range of human exposure.

When and how modeling can help: FIH, Phase 1

- **FIH (Dose-escalation) study:**
  - **Case 3:** use Q1W low-dose cohort data to predict exposure at Q3W high-dose regimens; Suggest dosing regimen that would provide trough level above the target for 90% of patients
  - **Result:** TMDD model was developed; model-based simulations were used to select Q3W dosing regimen with the desired trough levels.
- **Phase 1**
  - **Case 4:** two phase 1 studies in different populations gave inconsistent results. Diseases differed by target expression.
  - **Result:** A combined model was able to explain the observed data using the baseline target level as a covariate for the TMDD model parameters that characterize the target turnover.

When and how modeling can help: Phase 2

- **Phase 1 – Phase 2 – Phase 2b Transition, Stage 1**
  - **Case 5:** FIH PK and PD data were available. Design of the phase 2 study that would provide the desired trough level of the PD variable was requested.
  - **Result:** TMDD model described PK. Indirect response model described PD. Model-based simulations were used to design the optimal IV dosing regimen. Design parameters: dose level; inter-dose interval; dependence of chosen dose on the baseline level of the PD variable.

When and how modeling can help: Phase 2b

- **Phase 1 – Phase 2 – Phase 2b Transition, Stage 2**
  - **Case 6:** Phase 1 and Phase 2 PK and PD data following IV and SC dosing were available for subjects with and without background standard-of-care therapy. We were asked to design of an SC dosing regimen that would provide the desired trough level of the PD variable and evaluate influence of standard-of-care drugs on PK and PD.

When and how modeling can help: Phase 2b

- **Result:**
  - TMDD model with the 1st order absorption described PK and estimated SC bioavailability.
  - Indirect response model described PD.
  - PK and PD model parameters depended on standard-of-care concomitant medications in a mechanistically plausible way.
  - Simulations were used to design the optimal dosing regimen.
  - Design parameters: dose level; inter-dose interval; dependence of dose on the baseline level of the PD variable; fixed dose versus per-kg dose; titration scheme to avoid too high values of the PD variable.

When and how modeling can help

- **Mechanistic explanation of the PK-PD relationships**
  - **Case 7:** Linking interleukin-6 receptor blockade with tocilizumab and its hematological effects using a modeling approach [1].

Results:

- Two-target PK – sIL-6R - mIL-6R model was presented as a combination of the PK model with MM elimination, and PK-sIL-6R indirect response model with inhibition of elimination;
- Un-observed (estimated by the model) suppression of the free sIL-6R concentrations) was used to drive PK-PD models;
- sIL-6R – neutrophil and sIL-6R - platelet counts models successfully explained observed decrease and recovery of neutrophil and platelet counts.

[1] Leonid Gibiansky and Nicolas Frey, Journal of Pharmacokinetics and Pharmacodynamics, 2011, DOI: 10.1007/s10928-011-9227-z

Summary

- Model-based drug development is even more important for biologics than for small-molecule drugs since simple rules and intuition do not work for nonlinear biologics.
- TMDD model helps to understand and formalize PK and PD properties of biologics.
- Study design for biologics should always be based on modeling that can help at all stages of drug development program, from pre-clinical to FIH to Phase 2.

Acknowledgement

Results and ideas described in the talk were developed in collaboration with Ekaterina Gibiansky

Thank you for your attention
Questions?

Copies of the slides will be available at NBC web site or by request to LGibiansky@quantpharm.com