

PAGE Satellite Workshop:
Modeling Biologics with Target-Mediated Disposition

Leonid Gibiansky, Ekaterina Gibiansky
QuantPharm LLC

Organized by ICON Development Solutions

Date and Time:

08:30-17:30 June 10, 2014 (Tuesday)

Registration fees include

- Attendance to the course,
- Binder with the hard copy of slides
- USB drive with the slides, NONMEM control streams, output, and the diagnostic plots of the discussed models
- Breakfast (8:00-8:30 am), lunch (12:30-1:30 pm), and coffee breaks (10:30-10:45 am and 3:30-3:45 pm).

Hotel accommodation:

No hotel accommodation will be provided.

Sponsor: QuantPharm LLC and ICON

Instructors:

Dr. Leonid Gibiansky, QuantPharm LLC
Dr. Ekaterina Gibiansky, QuantPharm LLC

Workshop summary:

The 1-day workshop is intended for PK scientists with or without prior experience in population PK modeling of therapeutic proteins. It will provide an overview of the PK of biologics, introduce target-mediated drug disposition (TMDD) modeling concepts, and discuss some applications of TMDD modeling to drug development of biologics. We will start with the detailed introduction of the TMDD system. Equations that describe the TMDD process will be introduced and implicit and explicit assumptions of these equations will be reviewed. Characteristic features of the TMDD system will be demonstrated on the simulated examples. Data that are typically available for the analysis and assay properties will be reviewed. It will be demonstrated why TMDD models are often overparameterized and poorly identifiable. The hierarchy of TMDD approximations (rapid binding, quasi-steady-state, irreversible binding, and Michaelis-Menten) will be derived and discussed. Extensions of the TMDD equations to more general systems, including antibody-drug conjugates will be demonstrated. Experience-based recommendations for modeling of TMDD systems will be discussed and demonstrated on case studies. Nonmem control streams that implement TMDD equations and its approximations will be provided. Biological considerations for choice of TMDD approximations will be introduced. We will review allometric scaling for FIH exposure predictions, covariates that may influence PK properties of biologics, and possible drug-drug interactions. Methods for detection, evaluation and modeling of immunogenicity will be discussed. Use of different Nonmem estimation methods and parallelization for TMDD models will be reviewed.

Part I: TMDD Model and Equations

- Short introduction to biologics;
- PK properties of biologics as related to their binding to targets;
- Characteristic features of the target-mediated drug disposition;
- Introduction of a target-mediated drug disposition (TMDD) system of equations;

- Implicit and explicit assumptions and how they translate into the TMDD equations.
- Assay properties; importance and difficulties in assessing drug and target concentrations; free versus total drug and target concentration assays;
- Difficulties and possible solutions in application of TMDD;

Part II: TMDD Model Approximations: Derivations, Selection and Applications

- Review and derivation of the TMDD model approximations;
- TMDD and equations with Michaelis-Menten elimination;
- Hierarchy of approximations of the TMDD system;
- Identifiability of TMDD model parameters;
- Modeling of drugs with TMDD: how to select correct approximation;
- Biological considerations for choice of TMDD approximations;
- Case study that demonstrates application of the introduced concepts on the example of a population PK model development for a monoclonal antibody with soluble target;

Part III: Applications to Drug Development of Biologics

- TMDD approximations and indirect response model;
- TMDD model for drugs that bind to more than one target;
- Immunogenicity: detection, evaluation, and modeling;
- Modeling of antibody-drug conjugates;
- Subcutaneous absorption: modeling of absorption rate and bioavailability;
- Prediction of human PK from animal data;
- Covariates that could be important for PK of biologics;
- Drug-drug interactions for biologics;
- PK-PD modeling of biologics;

Part IV: Nonmem Implementation of the TMDD Equations

- PK-PD case study: tocilizumab example.
- Nonmem control streams for the full TMDD system and various approximations;
- Nonmem control streams for possible generalizations of the TMDD equations:
 - binding in tissues;
 - TMDD system for drugs that bind to two targets;
- Brief summary of experience using new estimation methods and parallelization for TMDD models;
- Brief review of the recent literature on TMDD modeling of biologics.
- Questions and answers session.