AAPS National Biotechnology Conference, May 22, 2012, San Diego, CA
Sunrise Session: Target-Mediated Drug Disposition: Opportunities, Practical Challenges and Pitfalls.

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

Abstract

Purpose: To introduce a target-mediated drug disposition (TMDD) model and its approximations, and discuss underlying assumptions and model properties; to describe use of modeling in design of FIH and Phase 1 trials, and in selection of dosing regimens and sampling schemes for Phase 2 trials.

Methods: The TMDD model describes biological processes where drug-target binding significantly influences both, pharmacodynamics (PD) and pharmacokinetics (PK). These are typical for the biologic drugs with high specificity to the intended target. Various TMDD approximations have been developed. These models are instrumental in the development of drugs with TMDD. Specifically, model-based analyses can help in selection of starting doses and dose escalation schemes in FIH trials, in prediction of human exposure based on pre-clinical data. Modeling facilitates the design of Phase 2 trials where model-based simulations can be used to select optimal dose levels and dosing frequency, optimal times of sampling, and can predict expected PK and PD results based on the available Phase 1 data. The talk will discuss ideas, examples, and experience-based recommendations for use of the TMDD models in drug development.

Results: Selection of the appropriate TMDD model requires understanding of the underlying biology and assumptions, careful examination of the available data and model diagnostics. When done properly, the TMDD models provide robust description of the PK and PD data. Preclinical data from relevant species, allometric scaling of model parameters combined with the in-vitro drug target binding and human target turnover data allows developing the initial human model and designing the FIH trials. Typically available Phase 1 data allow developing predictive TMDD models that facilitate the design of the Phase 2 trials. The TMDD model can also serve as an important framework that helps to interpret the observed covariate dependencies and drug interactions.

Conclusions: Modeling is instrumental in successful development of drugs with TMDD.