**Supplemental 1: Model Equations**

Full Target-Mediated Drug Disposition (TMDD) Model

*In(t)* refers to a continuous i.v. infusion

$$\frac{dA_d}{dt} = -k_a A_d \tag{1}$$

$$\frac{dC}{dt} = \frac{ln(t) + k_a A_d}{Vc} - (k_{el} + k_{pt})C - k_{on} C \cdot R + k_{off} RC + k_{tp} \frac{A_T}{Vc} \tag{2}$$

$$\frac{dA_T}{dt} = k_{pt} C \cdot Vc - k_{tp} A_T \tag{3}$$

$$\frac{dR}{dt} = k_{syn} - k_{deg} R - k_{on} C \cdot R + k_{off} RC \tag{4}$$

$$\frac{dRC}{dt} = k_{on} C \cdot R - (k_{int} + k_{off})RC \tag{5}$$

$$A_d = Dose; \quad C(0) = 0; \quad A_T(0) = 0; \quad RC(0) = 0; \quad R(0) = \frac{k_{syn}}{k_{deg}} \tag{6}$$

Equations from: D. E. Mager and W. J. Jusko. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. *J Pharmacokinet Pharmacodyn*, 28(6):507-532, Dec 2001.

Quasi-Equilibrum/Rapid Binding (QE/RB) Approximation

*In(t)* refers to a continuous i.v. infusion

$$C = \frac{1}{2}\left[(C_{tot} - R_{tot} - K_D) + \sqrt{(C_{tot} - R_{tot} - K_D)^2 + 4K_D C_{tot}}\right] \tag{7}$$

$$\frac{dC_{tot}}{dt} = \frac{ln(t)}{Vc} - k_{int}C_{tot} - (k_{el} + k_{pt} - k_{int})C + \frac{k_{tp}A_T}{Vc} \tag{8}$$

$$\frac{dA_T}{dt} = k_{pt}C \cdot Vc - k_{tp}A_T \tag{9}$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})(C_{tot} - C) \tag{10}$$

$$C_{tot}(0) = 0; \quad A_T(0) = 0; \quad R_{tot}(0) = \frac{k_{syn}}{k_{deg}} \tag{11}$$

Equations from: L. Gibiansky, E. Gibiansky, T. Kakkar, and P. Ma. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn*, 35(5):573-591, Oct 2008.

Quasi-Steady-State (QSS) Approximation

*In(t)* refers to a continuous i.v. infusion

$$C = \frac{1}{2}\left[(C_{tot} - R_{tot} - K_{SS}) + \sqrt{(C_{tot} - R_{tot} - K_{SS})^2 + 4K_{SS}C_{tot}}\right] \tag{12}$$

$$\frac{dC_{tot}}{dt} = \frac{ln(t)}{Vc} - (k_{el} + k_{pt})C - \frac{R_{tot}k_{int}C}{K_{SS} + C} + \frac{K_{tp}A_T}{Vc} \tag{13}$$

$$\frac{dA_T}{dt} = k_{pt}C \cdot Vc - k_{tp}A_T \tag{14}$$

$$\frac{dR_{tot}}{dt} = k_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})\frac{R_{tot}C}{K_{SS} + C} \tag{15}$$

$$C_{tot}(0) = 0; \quad A_T(0) = 0; \quad R_{tot}(0) = \frac{k_{syn}}{k_{deg}} \tag{16}$$

Equations from: L. Gibiansky, E. Gibiansky, T. Kakkar, and P. Ma. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn*, 35(5):573-591, Oct 2008.

Michaelis Menten (MM) Approximation

*In(t)* refers to a continuous i.v. infusion

$$\frac{dC}{dt} = \frac{ln(t)}{Vc} - (k_{el} + k_{pt})C - \frac{R_{tot}k_{int}}{K_m + C} + \frac{k_{tp}A_T}{Vc} \tag{17}$$

$$\frac{dA_T}{dt} = k_{pt}C \cdot Vc - k_{tp}A_T \tag{18}$$

$$\frac{dR_{tot}}{dt} = R_{syn} - k_{deg}R_{tot} - (k_{int} - k_{deg})\frac{R_{tot}C}{K_m + C} \tag{19}$$

$$C(0) = 0; \quad A_T(0) = 0; \quad R_{tot}(0) = \frac{k_{syn}}{k_{deg}} \tag{20}$$

Equations from: L. Gibiansky, E. Gibiansky, T. Kakkar, and P. Ma. Approximations of the target-mediated drug disposition model and identifiability of model parameters. *J Pharmacokinet Pharmacodyn*, 35(5):573-591, Oct 2008.

TMDD Extended to Two Targets

*In(t)* refers to a continuous i.v. infusion

$$\frac{dC}{dt} = \frac{k_{tp}A_T + In(t)}{Vc} - (k_{el} + k_{pt})C - (k_{on1}C \cdot R_1 + k_{on2}C \cdot R_2) + (k_{off1}R_1C + k_{off2}R_2C) \quad (21)$$

$$\frac{dA_T}{dt} = k_{pt}CVc - k_{tp}A_T \quad (22)$$

$$\frac{dR_1}{dt} = k_{syn1} - k_{deg1}R_1 - k_{on1}C \cdot R_1 + k_{off1}R_1C \quad (23)$$

$$\frac{dR_2}{dt} = k_{syn2} - k_{deg2}R_2 - k_{on2}C \cdot R_2 + k_{off2}R_2C \quad (24)$$

$$\frac{dR_1C}{dt} = k_{on1}C \cdot R_1 - (k_{int1} + k_{off1})R_1C \quad (25)$$

$$\frac{dR_2C}{dt} = k_{on2}C \cdot R_2 - (k_{int2} + k_{off2})R_2C \quad (26)$$

$$C(0) = 0;\ \ A_T(0) = 0;\ \ R_1(0) = \frac{k_{syn1}}{k_{deg1}};\ \ R_2(0) = \frac{k_{syn2}}{k_{deg2}};\ \ R_1C(0) = 0;\ \ R_2C(0) = 0 \quad (27)$$

Equations from: L. Gibiansky and E. Gibiansky. Target-mediated drug disposition model for drugs that bind to more than one target. *J Pharmacokinet Pharmacodyn*, 37(4):323-46, Aug 2010.