PHA5127 – Fall 2005
Homework #5 Answer Key (10 points)

Please show all your calculations and make sure your numerical answers have units.

1. **Benjamin is given an i.v. bolus injection of Drug A. Below are the properties of the drug:**

Volume of distribution	**400 L**
Clearance	**130 mL/min**
Therapeutic range	**1 – 2 mg/L**

Calculate a dosing regimen (multiple IV doses) that will maintain the serum drug concentrations within the therapeutic range. (2pts; Two answer choices possible)

$$CL = k_e \cdot V_d$$

$$k_e = \frac{CL}{V_d} = \frac{\left(130\,{}^{mL}\!/_{\min}\right)\left(\frac{60\min}{1h}\right)\left(\frac{1L}{1000mL}\right)}{400L} = 0.0195h^{-1}$$

$$F = \frac{Cp_{ss,\max}}{Cp_{ss,\min}} = \frac{2\,{}^{mg}\!/_{L}}{1\,{}^{mg}\!/_{L}} = 2$$

$$\tau = \frac{\ln(F)}{k_e} = \frac{\ln(2)}{0.0195h^{-1}} = 35.5h \sim 36h$$

$$\overline{C}p_{ss} = \frac{D}{CL \cdot \tau}$$

$$D = \overline{C}p_{ss} \cdot CL \cdot \tau = 1.5\,{}^{mg}\!/_{L} \cdot \left(130\,{}^{mL}\!/_{\min}\right)\left(\frac{60\min}{1h}\right)\left(\frac{1L}{1000mL}\right) \cdot 36h = 420mg$$

Or for a more patient compliant dosing regimen, once a day dosing would be better.

$$\tau = 24h$$

$$D = \overline{C}p_{ss} \cdot CL \cdot \tau = 1.5\,{}^{mg}\!/_{L} \cdot \left(130\,{}^{mL}\!/_{\min}\right)\left(\frac{60\min}{1h}\right)\left(\frac{1L}{1000mL}\right) \cdot 24h = 280mg$$

So Benjamin would be given a 420mg (1pt) i.v. bolus injection every 36hrs (1pt).
OR
For a more patient compliant dosing regimen: 280mg (1pt) every 24hrs (1pt).

2. **For the following scenarios for a multiple dose i.v. bolus therapy, determine what will happen to the average steady-state concentration, the peak concentration, and the fluctuation. Use arrows to indicate if it increases, decreases, or stays the same.** *Use 'Multiple IV bolus injection' simulation.*(4pts)

a) The clearance is doubled. (0.33pt for each answer; 1pt total)

b) The volume of distribution is halved. (0.33pt for each answer; 1pt total)
c) The dose is doubled. (0.33pt for each answer; 1pt total)
d) The number of doses given per a day is halved. *So τ doubles.* (0.33pt for each answer; 1pt total)

	$C_{avg,ss}$	C_{max}	F
a) CL	↓	↓	↑
b) V_d	↔	↑	↑
c) D	↑	↑	↔
d) # of D	↓	↓	↑

3. **True/False: Please state if each of the following is true or is false.** (4pts; 1 each)
   a) The shorter dosing interval, the higher steady state average concentration.
   True. $C_{avg,ss} = \dfrac{D}{CL \cdot \tau}$
   b) The higher half-life, the larger fluctuation. **False.**
   $\uparrow t_{1/2} = \downarrow k_e \qquad F = \dfrac{C_{\max}}{C_{\min}} = e^{k_e \cdot \tau}$
   c) The shorter the half-life, the smaller degree of accumulation. **True.**
   $\downarrow t_{1/2} = \uparrow k_e \qquad R_{ss} = \dfrac{1}{\left(1 - e^{-k_e \cdot \tau}\right)}$
   d) The longer dosing interval, the longer to achieve steady state. **False. Time to achieve steady state is about 5 half-lives.**