Name: _____

UFID#: _____

PHA 5127

Final Exam

Fall 2012

On my honor, I have neither given nor received unauthorized aid in doing this assignment.

Name

Please transfer the answers onto the bubble sheet. The question number refers to the number on the bubble sheet. Please fill in all the information necessary to identify yourself. The proctors will also collect your exams.

Good LUCK.

Question/ ---Points

TOTAL _____110_/pts

Name: _____

UFID#: _____

Question Set I (10 pts)**:** Select whether the following statements are True (A) or False (B)

1:	T	F	For bioequivalence tests, AUC is a relevant measure to assess whether test and reference formulation deliver the same dose.
2:	T	F	For bioequivalence tests, AUC is a relevant measure to assess whether test and reference formulation have the same volume of distribution.
3:	T	F	For bioequivalence tests, AUC is a relevant measure to assess whether test and reference formulation have the same rate of absorption.
4:	T	F	For bioequivalence tests, C_{max} is a relevant measure to assess whether test and reference formulation have the same rate of absorption.
5:	T	F	For bioequivalence tests, C_{max} differs between test and reference formulation if both deliver different doses (assume same rate of absorption for both formulations).

Name: _____

UFID#: _____

Question set II (6 pts)**:**

Select from the following statements whether the statements are True (A) or False (B).

6: T F Assume steady state has been reached after having started a constant rate infusion. At steady state, k_0 will equal intrinsic clearance.

7: T F The time to reach steady state after a constant rate infusion is affected by the k_e of the drug.

8: T F Assume a drug given as iv bolus every 8 hours. It was observed that the C_{max} does not differ between the first three injections. The half-life of this drug is shorter than 2 hours.

Question Set III (4 pts)**:**

Select from the following statements whether the statements are True (A) or False (B).

Assume a multiple dosing situation.

9: T F For a lipophilic drug whose clearance is constant under the given conditions, the following statement can be made: The stronger the tissue binding the more pronounced the degree of accumulation.

10: T F For a lipophilic drug whose clearance is constant under the given conditions, the following statement can be made: The stronger the tissue binding the smaller the fluctuation between peak and trough concentration.

Name: _____

UFID#: _____

Question Set IV (15 pts)**:**

Patient TK, a 65 kg, 17 yr old boy, has been given a constant rate infusion of theophylline for an acute asthma attack. The infusion rate is 30 mg/hr. His plasma theophylline level is now 12 μg/ml.

Question 11: Assume steady state has been reached. Calculate TK's clearance. **Round appropriately**. (5 pts)

A: 2.5 L/hr

B: 2.5 L/ 0.5 hours

C: 2.5 L

D: 2.5 mg/hr

E: none of the above

Name: _____

UFID#: _____

Patient TK, a 65 kg, 17 yr old boy, has been given a constant rate infusion of theophylline for an acute asthma attack. The infusion rate is 30 mg/hr. His plasma theophylline level is now 12 µg/ml.

Question 12: The doctor wants to change to an oral delivery. Assume an oral bioavailability of 100% for theophylline. Suggest an oral dosage regimen that will produce an average steady state concentration of 12 **µ**g/ml, using a *sustained release product*, dosed every 12 hours (twice a day). Give the dose in mg of theophylline. There are only 100 mg tablets available. Consider that the therapeutic range is between 10 and 20 µg/ml. **Round appropriately**. (5 pts)

A: 200 mg every 12 hours

B: 300 mg every 12 hours

C: 400 mg every 12 hours

D: 500 mg every 12 hours

E: 600mg every 12 hours

Name: _____

UFID#: _____

Patient TK, a 65 kg, 17 yr old boy, has been given a constant rate infusion of theophylline for an acute asthma attack. The infusion rate is 30 mg/hr. His plasma theophylline level is now 12 μg/ml. **Round appropriately**

Question 13: Assuming a Vd of 0.5 L/kg, what is the half-life in this patient after an iv bolus injection (assume first order elimination and one compartment body model). (5 points)

A: 12 hours

B: 9 hours

C: 24 hours

D: 16 hours

E: None of the above.

Name: _____

UFID#: _____

Question Set V (5 pts)

Question 14: A 60 kg patient is started on 80 mg of gentamicin, every 6 hr given as a one-hour infusion. Assume that steady state has been reached for this multiple dosing situation. If this patient is assumed to have an "average" volume of distribution (value of the population mean) of 0.25 L/kg and a normal half–life of 3 hr, what would be the plasma concentration **1 hour after the stop of the infusion**? **Round appropriately**. (5 points)

A: 3.2 mg/L

B: 2.5 mg/L

C: 0.8 mg/L

D: 1.2 mg/L

E: None of the above

Name: _____

UFID#: _____

Question Set VI (7 points)

Question 15: A 60 kg patient should receive 80 mg of drug X, every 6 hr given as a one-hour infusion. The half-life of this drug is 4 hours. Calculate a loading dose given as short-term infusion over 1 hour for this scenario.

A: 100 mg

B: 200 mg

C 300 mg

D: 400 mg

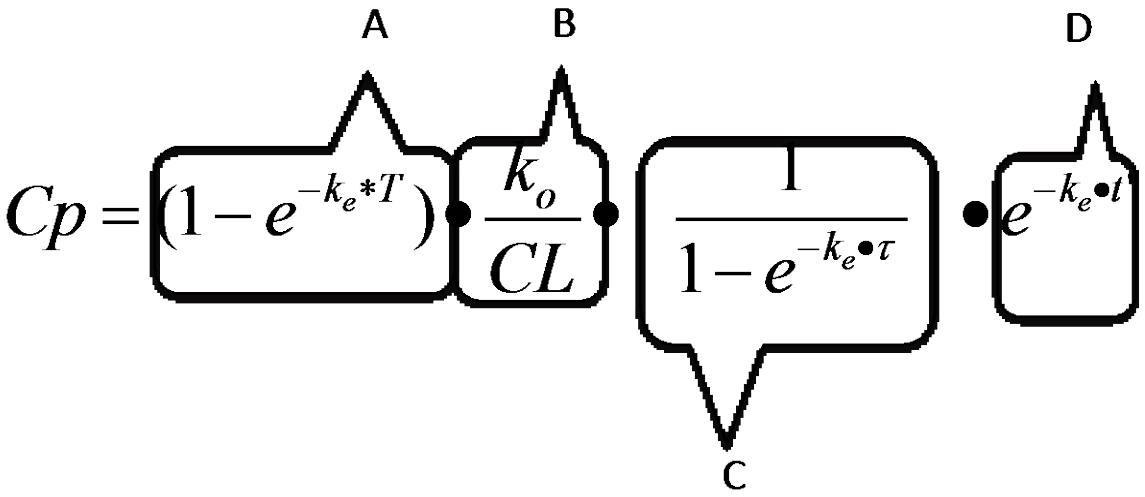
E: Don't have enough information to provide this information.

Name: _____

UFID#: _____

Question Set VII (12 pts)

Consider the following equation:



- "Number between 1 and 0" means that for time units (T, t' or tau) being 0, the relevant expression will be 1. The expression will approach 0 for large time unit values.
- "Number between 0 and 1" means that for time units (T, t' or tau) being 0, the relevant expression will be 0. It will approach 1 for large time unit values.

Select the part of the equation (A, B, C, D) that best the following statements:

16: This part of the equation provides information on what concentrations would be observed in a patient for which the nurse forgot to turn off the drug supply.

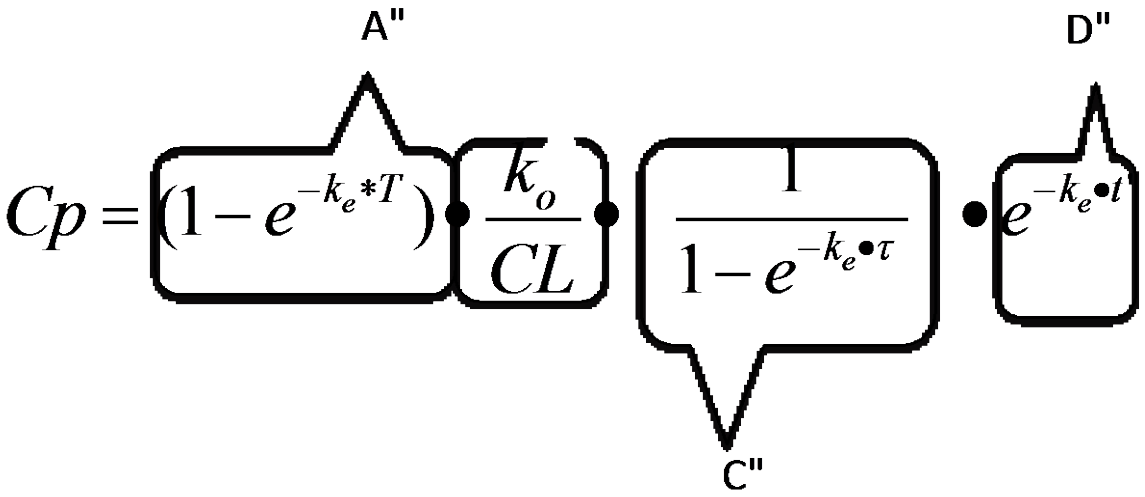
17: This part of the equation provides information on how much the first C_{max} (after the first short term infusion) is away from the steady level of a continuous infusion using the same k_o.

18: This part quantifies how much higher the trough concentrations at steady state are compared to the trough concentration after the first dose.

Name: _____

UFID#: _____

Consider the same equation equation:



Consider:

- "Number between 1 and 0" means that for time units (T, t' or tau) being 0, the relevant expressing will be 1. The expression will approach 0 for large time unit values.
- "Number between 0 and 1" means that for time units (T, t' or tau) being 0, the relevant expressing will be 0. It will approach 1 for large time unit values.

Select the part of the equation **(A, C, or D)** that best the following statements:

19: This part of the equation is a number between 1 and infinity.

20: This part of the equation is a number between 0 and 1.

21: This part of the equation is a number between 1 and 0.

Name: _____

UFID#: _____

Question Set VIII (8 pts)

Consider the following relationship.

$$tau = \frac{Vd * \ln F}{Cl}$$

22: T F F stands for oral bioavailability

23: T F This term indicates that the higher the clearance and/or the smaller VD of a drug, the shorter will be the dosing interval necessary to maintain a given C_{max}/C_{min} ratio

24: T F This relationship can be used to calculate the dosing interval for multiple short-term infusions if one adds the infusion time to the above expression.

25: T F This term should only be used for a drug after oral administration

Name: _____

UFID#: _____

Question Set IX (12 points)

Question 26-31: Two patients received a **lipophilic, unionized drug,** as an iv bolus injection. Pharmacokinetic and physiological characteristics, such as dose, fraction of the drug unbound in plasma (fu) and tissue (fuT), volume of plasma (Vp) and volume of the tissue water (VTW) are shown below.

TABLE 1: INPUT PARAMETERS

	Patient 1	Patient 2
D [mg]	40	40
GFR (ml/min)	120	60
Urine flow (ml/min)	1	1
fu	0.5	1.0
fuT	0.5	0.5
Vp [L]	3	3
VTW [L]	38	38

Indicate which of the following parameters (questions 26- 31) in patient 2 will be clearly larger (A), be ABOUT the same (B), or will be clearly smaller (C) than those in **Patient 1.**

Table 2: OUTPUT PARAMETERS

Question:		
26. (2 points)	**Vd [L] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
27. (2 points)	**CL [L/h] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
28. (2 points)	**t1/2 [h] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
29. (2 points)	**Peak [μg/ml] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
30. (2 points)	**AUC [μg/ml*h] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1
31. (2 points)	**Free drug concentration at t=0 [μg/ml] of Patient 2**	Larger (A), same (B), Smaller (C) than in Patient 1

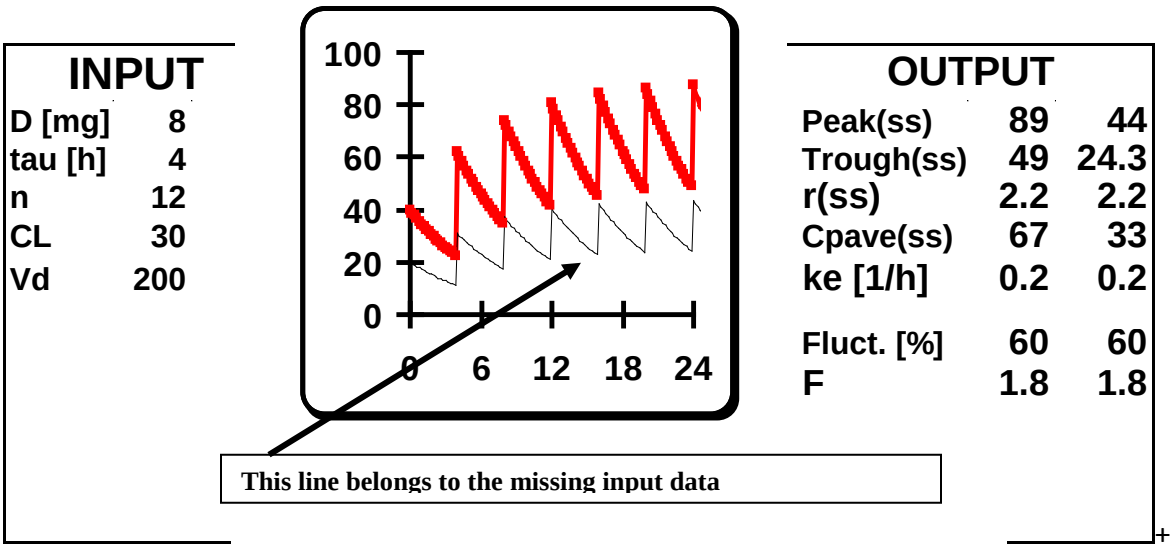
Name: _____

UFID#: _____

Question Set X (5 points)

Question 32:

The following concentration time profiles were observed after multiple iv bolus injections of a drug. The two curves differ in one of the input parameters (Dose, tau, CL or Vd).



Identify the one input parameter that differs (question 32)

A: Dose

B: Clearance

C: Volume of distribution

D: tau

E: none of the above

Name: _____

UFID#: _____

Question Set XI (5 pts)

Question 33: Which of the following factors might significantly affect(s) the renal clearance of a hydrophilic base (pKa=7):

1. plasma protein binding.
2. activity of cationic transporters in the tubuli.
3. urine flow.
4. pH of urine.
5. GFR.

A: 1, 2, 3, 5

B: 1, 2

C: 1, 5

D: 1, 3, 4, 5

E: none of the above combinations

Name: _____

UFID#: _____

Question Set XII (12 points)

Questions 34-37

Assume first-order processes. Mark whether the following statements are true (A) or false (B).

34: T F A drug is eliminated through liver metabolism and renal clearance. The overall elimination rate constant for this drug is 0.5 h^{-1}. The rate constant for metabolism (k_{met}) is 0.1. This indicates that 80% of the dose will be eliminated unmetabolized.

35: T F Assume that a drug is metabolized. The K_e^M of the metabolite is 20 h^{-1} while the k_e of the parent drug is 0.231 h^{-1}. If the plasma concentrations 10 hours after injection of the parent drug are 1 µg/ml for the parent drug and 0.5 µg/ml for the metabolite, the plasma concentrations 13 hours after injection of the parent drug must be 0.5 µg/ml for the parent drug and undetectable for the metabolite. (Assume first-order kinetics for all elimination processes, lowest concentration measurable with the drug assay is 0.01 µg/ml.)

36: T F For a two-compartment model drug, the volume of distribution just after administration of the drug is larger than that observed some time later.

37: T F For a two compartment body model, Clearance and volume of distribution are always independent parameters.

Name: _____

UFID#: _____

Question Set XIII

Questions 38-40 (9 points)

Select the most appropriate differential equation for the following situations. A given differential equation might have to be used more than once. Assume "**X"** is the amount of drug in the body (drug that has been absorbed and has not yet been eliminated) and "**A"** is the amount left at the absorption site.

A: $dx/dt = k_a - k_e$

B: $dx/dt = -k_a - k_e * X$

C: $dx/dt = k_a * A - k_e * X$

D: $dx/dt = - k_e$

E: none of the above

38: A drug that is absorbed and eliminated through active transport. Both transporter systems are saturated. (Select from A-E)

39: An immediate release tablet of a drug able to cross membranes easily and eliminated through renal filtration. (Select from A-E)

40: A high extraction drug given as an iv bolus injection showing linear pharmacokinetics. (Select from A-E)

Useful Pharmacokinetic Equations

Symbols

D = dose
τ = dosing interval
CL = clearance
Vd = volume of distribution
k_e = elimination rate constant
k_a = absorption rate constant
F = fraction absorbed (bioavailability)
K_0 = infusion rate
T = duration of infusion
C = plasma concentration

General

Elimination rate constant

$$k_e = \frac{CL}{Vd} = \frac{\ln\left(\frac{C_1}{C_2}\right)}{(t_2 - t_1)} = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)}$$

Half-life

$$t_{1/2} = \frac{0.693 \cdot Vd}{CL} = \frac{\ln(2)}{k_e} = \frac{0.693}{k_e}$$

Intravenous bolus

Initial concentration

$$C_0 = \frac{D}{Vd}$$

Plasma concentration (single dose)

$$C = C_0 \cdot e^{-k_e \cdot t}$$

Plasma concentration (multiple dose)

$$C = \frac{C_0 \cdot e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Peak (multiple dose)

$$C_{max} = \frac{C_0}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = \frac{C_0 \cdot e^{-k_e \cdot \tau}}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Average concentration (steady state)

$$\overline{Cp}_{ss} = \frac{D}{CL \cdot \tau}$$

Oral administration

Plasma concentration (single dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(e^{-k_e \cdot t} - e^{-k_a \cdot t}\right)$$

Time of maximum concentration (single dose)

$$t_{max} = \frac{\ln\left(\frac{k_a}{k_e}\right)}{(k_a - k_e)}$$

Plasma concentration (multiple dose)

$$C = \frac{F \cdot D \cdot k_a}{Vd(k_a - k_e)} \cdot \left(\frac{e^{-k_e \cdot t}}{\left(1 - e^{-k_e \cdot \tau}\right)} - \frac{e^{-k_a \cdot t}}{\left(1 - e^{-k_a \cdot \tau}\right)}\right)$$

Time of maximum concentration (multiple dose)

$$t_{max} = \frac{\ln\left(\frac{k_a \cdot \left(1 - e^{-k_e \cdot \tau}\right)}{k_e \cdot \left(1 - e^{-k_a \cdot \tau}\right)}\right)}{(k_a - k_e)}$$

Average concentration (steady state)

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

Clearance

$$Cl = \frac{Dose \cdot F}{AUC}$$

$$Cl = k_e \cdot V_d$$

Constant rate infusion

Plasma concentration (during infusion)

$$C = \frac{k_0}{CL} \cdot \left(1 - e^{-k_e \cdot t}\right)$$

Plasma concentration (steady state)

$$C = \frac{k_0}{CL}$$

Calculated clearance (Chiou equation)

$$CL = \frac{2 \cdot k_0}{(C_1 + C_2)} + \frac{2 \cdot Vd \cdot (C_1 - C_2)}{(C_1 + C_2) \cdot (t_2 - t_1)}$$

Short-term infusion

Peak (single dose)

$$C_{max(1)} = \frac{D}{CL \cdot T} \cdot \left(1 - e^{-k_e \cdot T}\right)$$

Trough (single dose)

$$C_{min(1)} = C_{max(1)} \cdot e^{-k_e \cdot (\tau - T)}$$

Peak (multiple dose)

$$C_{max} = \frac{D}{CL \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{\left(1 - e^{-k_e \cdot \tau}\right)}$$

Trough (multiple dose)

$$C_{min} = C_{max} \cdot e^{-k_e \cdot (\tau - T)}$$

Calculated elimination rate constant

$$k_e = \frac{\ln\left(\frac{C^*_{max}}{C^*_{min}}\right)}{\Delta t}$$

with C_{max}^* = measured peak and C_{min}^* = measured trough,
measured over the time interval Δt

Calculated peak

$$C_{max} = \frac{C^*_{max}}{e^{-k_e \cdot t^*}}$$

with C_{max}^* = measured peak, measured at time t^* after the end of the infusion

Calculated trough

$$C_{min} = C^*_{min} \cdot e^{-k_e \cdot t^*}$$

with C_{min}^* = measured trough, measured at time t^* before the start of the next infusion

Calculated volume of distribution

$$Vd = \frac{D}{k_e \cdot T} \cdot \frac{\left(1 - e^{-k_e \cdot T}\right)}{[C_{max} - (C_{min} \cdot e^{-k_e \cdot T})]}$$

Calculated recommended dosing interval

$$\tau = \frac{\ln\left(\frac{C_{max(desired)}}{C_{min(desired)}}\right)}{k_e} + T$$

Calculated recommended dose

$$D = C_{max(desired)} \cdot k_e \cdot V \cdot T \cdot \frac{\left(1 - e^{-k_e \cdot \tau}\right)}{\left(1 - e^{-k_e \cdot T}\right)}$$

Two-Compartment-Body Model

$$C = a \bullet e^{-\alpha t} + b \bullet e^{-\beta t}$$

$$AUC_{\infty} = a / \alpha + b / \beta$$

$$Vd_{area} > Vd_{ss} > Vc$$

Creatinine Clearance

$$CL_{creat}(male) = \frac{(140 - age) \bullet weight}{72 \bullet Cp_{creat}}$$

$$CL_{creat}(female) = \frac{(140 - age) \bullet weight}{85 \bullet Cp_{creat}}$$

With weight in kg, age in years, creatinine plasma conc. in mg/dl and CL_{creat} in ml/min

K_e for aminoglycosides

$K_e = 0.00293(CrCL) + 0.014$

Metabolic and Renal Clearance

$$E_H = \frac{Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_H = E_H \cdot Q_H = \frac{Q_H \cdot Cl_{int} \cdot fu_b}{Q_H + Cl_{int} \cdot fu_b}$$

$$F_H = \frac{Q_H}{Q_H + Cl_{int} \cdot fu_b}$$

$$Cl_{ren} = RBF \cdot E = GFR \cdot \frac{C_{in} - C_{out}}{C_{in}}$$

$$Cl_{ren} = \frac{\text{rate of excretion}}{\text{plasma concentration}}$$

$$Cl_{ren} = fu \cdot GFR + \left[\frac{\text{Rate of secretion - Rate of reabsorption}}{\text{Plasma concentration}} \right]$$

$$Cl_{ren} = \frac{\text{Urine flow} \cdot \text{urine concentration}}{\text{Plasma concentration}}$$

Ideal Body Weight

Male
IBW = 50 kg + 2.3 kg for each inch over 5ft in height

Female
IBW = 45.5 kg + 2.3 kg for each inch over 5ft in height

Obese
ABW = IBW + 0.4*(TBW-IBW)

Volume of Distribution

$$V = V_P + V_T \cdot K_P$$

$$V = V_P + V_T \cdot \frac{fu}{fu_T}$$

Clearance

$$Cl = \frac{Dose}{AUC}$$

$$Cl = k_e \cdot V_d$$

For One Compartment Body Model

<table>
<tr>
<td>If the dosing involves the use of I.V. bolus administration:</td>
<td>
For a single I.V. bolus administration:
$$C_0 = \frac{D}{V}$$
$$C = C_0 \cdot e^{-k_e t}$$
</td>
<td>
For multiple I.V. bolus administration:
$$Cn(t) = \frac{D}{V} \cdot \frac{\left(1 - e^{-nk_e\tau}\right)}{\left(1 - e^{-k_e\tau}\right)} \cdot e^{-k_e t}$$
at peak: t = 0; at steady state n$\rightarrow\infty$
at trough: t = τ
$$C_{\max ss} = \frac{D}{V} \cdot \frac{1}{(1 - e^{-k_e\tau})}$$
$$C_{\min ss} = C_{\max ss} \cdot e^{-k_e\tau}$$
</td>
</tr>
<tr>
<td>If the dosing involves the use of I.V. infusion:</td>
<td>
For a single short-term I.V. infusion:
Since τ = t for C_{max}
$$C_{\max} = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_eT}\right)$$
$$C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$$
</td>
<td>
For multiple short-term I.V. infusion at steady state:
$$C_{\max} = \frac{D}{Vk_eT} \cdot \frac{\left(1 - e^{-k_eT}\right)}{\left(1 - e^{-k_e\tau}\right)}$$
$$C_{\min} = C_{\max} \cdot e^{-k_e(\tau - T)}$$
</td>
</tr>
</table>

If the dosing involves a I.V. infusion (more equations):

$$C_t = \frac{D}{Vk_eT} \cdot \left(e^{k_eT} - 1\right) \cdot e^{-k_et}$$ (most general eq.) during infusion t = T so,

$$C_t = \frac{D}{Vk_eT} \cdot \left(1 - e^{-k_et}\right)$$ (during infusion) at steady state $t \to \infty$, e^{-k_et}, $t \to 0$ so,

$$Cpss = \frac{D}{Vk_eT} = \frac{k_0}{Vk_e} = \frac{k_0}{CL}$$ (steady state) remembering $k_0 = \frac{D}{T}$ and

$$CL = V \cdot k_e$$

If the dosing involves oral administration:

For a single oral dose:

$$C = \frac{F \cdot D \cdot k_a}{V\left(k_a - k_e\right)} \cdot \left(e^{-k_et} - e^{-k_at}\right)$$

$$t_{\max} = \ln\left[\frac{k_a}{k_e}\right] \cdot \frac{1}{\left(k_a - k_e\right)}$$

For multiple oral doses:

$$C = \frac{F \cdot D \cdot k_a}{V\left(k_a - k_e\right)} \cdot \left[\frac{e^{-k_et}}{\left(1 - e^{-k_e\tau}\right)} - \frac{e^{-k_at}}{\left(1 - e^{-k_}\right.}\right.$$

$$t_{\max} = \ln\left[\frac{k_a \cdot \left(1 - e^{-k_e\tau}\right)}{k_e \cdot \left(1 - e^{-k_a\tau}\right)}\right] \cdot \frac{1}{\left(k_a - k_e\right)}$$