Please provide all answers with their appropriate units. 0.5 points will be deducted for each missing or inappropriate unit. Please show how you found your answers. If you do not show your work and your answer differs from the right solution, no points will be given. This homework is due Feb. 21st.

Question 1

A.Z. a 42-year old, 62.5 kg female will receive carbamazepine tablets. Please calculate a daily oral dose to achieve average steady plasma concentration of 6 mg/L for monotherapy (1 pt)

Carbamazepine has a clearance of 0.064 L/kg/h for monotherapy. For immediate release carbamazepine, the oral bioavailability is 0.8

\[
D = \frac{C_{ss} \times CL \times \tau}{F \times S} = \frac{6 \times 0.064 \times 62.5 \times 24}{0.8 \times 1} = 720 \text{ mg}
\]
Question 2

B.Z. is a 58-year old, 67 kg male and will take valproic acid tablets. In a previous trial of a single dose of 500 mg in this patient, it was found that an initial concentration of 48 μg/ml had been reduced to 14 μg/ml within 24hr. Suggest a dosing regimen for her treatment to maintain concentration within range from 50 to 100 mg/L. (2 pts)

\[
\tau = \frac{\ln(C_{\text{max,desired}})}{k_e} = \frac{\ln\left(\frac{100}{50}\right)}{0.051} = 13.59 \text{ h } \approx 12 \text{ h } (1\text{pt})
\]

\[
k_e = \frac{\ln\left(\frac{C_1}{C_2}\right)}{t_2 - t_1} = \frac{\ln\left(\frac{48}{10}\right)}{24} = 0.065 \text{ h}^{-1}
\]

The volume distribution is assumed to be 0.14 L/kg

\[
V_d = 0.14 \times 67 = 9.38 \text{ L}
\]

\[
C_{\text{ss, max}} = \frac{F \times S \times D}{V_d \times \left(1 - e^{-k_e \times \tau}\right)}
\]

\[
D = \frac{C_{\text{ss, max}} \times V_d \times (1 - e^{-k_e \times \tau})}{F \times S} = \frac{100 \times 9.38 \times (1 - e^{-0.065 \times 12})}{1 \times 1} = 508 \text{ mg } \approx 500 \text{ mg } (1\text{pt})
\]

The dose regimen is 500 mg every 12 hrs

Or

\[
D = \frac{C_{\text{ss, min}} \times V_d \times (1 - e^{-k_e \times \tau})}{F \times S \times e^{-k_e \times \tau}} = \frac{50 \times 9.38 \times (1 - e^{-0.065 \times 12})}{1 \times 1 \times e^{-0.065 \times 12}} = 554 \text{ mg } \approx 500 \text{ mg } (1\text{pt})
\]
Question 3

A patient (35-year old, 68 kg) is to be started on phenobarbital sodium. (3 pts)

a. Calculate a loading dose to yield plasma concentration of 20 mg/L.

The volume distribution is assumed to be 0.7 L/kg for adults

\[ LD = \frac{C_p \times V_d}{F \times S} = \frac{20 \times 0.7 \times 68}{1 \times 0.9} = 1057.8 \, mg \approx 1g \] (1pt)

b. Calculate a daily maintenance dose to produce an average steady state concentration of 20 mg/L.

The clearance is assumed to be 0.004 L/kg/h for adults

\[ MD = \frac{C_{pss} \times CL \times \tau}{F \times S} = \frac{20 \times 0.004 \times 68 \times 24}{1 \times 0.9} = 145 \, mg \] (1pt)

c. The same patient is to be treated simultaneously with carbamazepine. Propose an oral maintenance dosing regimen for carbamazepine for this patient to achieve a carbamazepine level of 6 μg/mL.

Carbamazepine has a clearance of 0.1 L/kg/h for polytherapy. For immediate release carbamazepine, the oral bioavailability is 0.8

\[ MD = \frac{C_{pss} \times CL \times \tau}{F \times S} = \frac{6 \times 0.1 \times 58 \times 24}{1 \times 0.8} = 1044 \, mg \]

Carbamazepine dose regimen for this patient is 500 mg every 12 hrs. (1pt)
Question 4

50-year old, 68 kg male has been receiving 200mg/day (100 mg BID) of phenobarbital (S=1) for the past 25 days. Please calculate the phenobarbital plasma concentration just before the morning dose on Day 26. (2 pts)

The volume distribution and clearance is assumed to be 0.7 L/kg and 0.004 L/kg/h for adults, respectively.

\[ k_e = \frac{CL}{V_d} = \frac{0.004 \times 68}{0.7 \times 68} = 0.0057 \text{ } h^{-1} \]  

(1pt)

\[ t_{1/2} = \frac{0.693}{k_e} = \frac{0.693}{0.0057} = 121.58 \text{ } h \approx 5.05 \text{ } days \]

Phenobarbital should be achieved steady-state on Day 26.

\[ C_{ss} = \frac{S \times F \times D}{CL \times \tau} = \frac{1 \times 1 \times 100}{0.004 \times 68 \times 12} = 30.64 \text{ } mg/L \]

\[ C_{ss, min} = \frac{F \times S \times D \times e^{-k_e \tau}}{V_d \left(1 - e^{-k_e \tau}\right)} = \frac{1 \times 1 \times 100 \times e^{-0.0057 \times 12}}{0.7 \times 68 \left(1 - e^{-0.0057 \times 12}\right)} = 29.66 \text{ } mg/L \]  

(1pt)
Question 5

A recent study was performed to investigate the effects of ketoconazole and carbamazepine on the pharmacokinetics of Drug X. Drug X was given to the subjects alone, or co-administration of ketoconazole or carbamazepine. The plasma concentration of Drug X is presented in the following Figures. Which of the following statement is FALSE? And WHY? (2 pts)

**A)** In this study, ketoconazole increased mean Drug X plasma $C_{\text{max}}$ significantly; and Carbamazepine decreased mean Drug X plasma $C_{\text{max}}$ dramatically.

**B)** Cytochrome P450 3A4 is a primary enzyme responsible for the metabolic clearance of Drug X.

**C)** Ketoconazole is the strong inhibitor of CYP3A4, and carbamazepine is the strong inducer of CYP 3A4.

**D)** Other drugs and ingested natural products that strongly modulate the activity or expression of CYP3A4 would be predicted to change exposure to Drug X.

**E)** Clearance of Drug X is increased by ketoconazole; and decreased by carbamazepine.

**Answer:** E (1pt)

**Inhibition of CYP3A4 decreases clearance; and induction of CYP3A4 increase clearance.** (1pt)