1. Define the pharmacokinetic parameters $V_{dss}$ and $V_{darea}$ and explain why $V_{dss}$ is always smaller than $V_{darea}$. 2 pts

$V_{dss}$: Volume of distribution at steady state
Central and peripheral compartment are in equilibrium (equal unbound concentrations)

$V_{darea}$: Volume of distribution during the elimination phase. There is a concentration gradient from the peripheral to the central compartment. (unbound concentration is higher in the peripheral compartment, lower in the central compartment)
Lower concentration in central compartment $\rightarrow$ larger $Vd$

Hence $V_{dss} < V_{darea}$

2a. What are the two pharmacokinetic parameters that are evaluated in a bioequivalence study whose log-transformed ratios (test:reference) must pass the two one-sided test about the 90% confidence intervals, and which one characterizes the extent of availability of the drug? 1 pts

AUC and Cmax

AUC $\rightarrow$ extent

2b. What is the lower and upper value of this interval?

80- 125 % or 0.80 – 1.25

3. Show for both high and low extraction drugs, how doubling the protein binding will affect the resulting unbound and total serum levels. What recommendations would you make for dose adjustments? Assume constant rate infusions and steady state. 2 pt

<table>
<thead>
<tr>
<th></th>
<th>High extraction drugs</th>
<th>Low extraction drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL</td>
<td>$Q(-)$</td>
<td>$fu \cdot CL_{int} (\downarrow)$</td>
</tr>
<tr>
<td>Css</td>
<td>$Ro/Q (-)$</td>
<td>$Ro/ (fu \cdot CL_{int}) (\uparrow)$</td>
</tr>
<tr>
<td>$fu*Css$ ( Free Css)</td>
<td>$Ro\cdot fu/Q(\downarrow)$</td>
<td>$Ro/Clint (-)$</td>
</tr>
<tr>
<td>Dose</td>
<td>$(\uparrow)$</td>
<td>(-)</td>
</tr>
</tbody>
</table>

$(\uparrow)$ increase
(-) no change
(\downarrow) decrease
4. Calculate the extraction ratio of phenylbutazone in a 70 kg patient, given the following information: liver blood flow, 1500 mL/min; half-life, 50 h; Vd, 0.1 L/kg; no non-hepatic elimination. 3 pts

For hepatic clearance,

$$Cl_H = E_H \cdot Q_H$$

Where $E_H$ is the extraction ratio and $Q_H$ is hepatic blood flow. In order to calculate $E_H$ using this expression, we must know $Cl_H$. Although $Cl_H$ is not given, enough information is provided to calculate it.

For a 70 kg patient,

$$Vd=0.1L/kg \times 70kg = 7L$$

The half-life may be used to find $k_e$.

$$k_e = \frac{\ln 2}{t_{1/2}} = \frac{0.693}{50hr} = 0.0139hr^{-1}$$

Clearance may now be calculated:

$$Cl = k_e \cdot Vd$$

$$= (0.0139 hr^{-1}) \cdot (7.0L) = 1.62mg/min$$

Actually, total body clearance is calculated from this expression. Since the problem states "no non-hepatic elimination", we may assume $Cl_H = 1.62$ ml/min.

The extraction ratio is then

$$E_H = \frac{CL_H}{Q_H} = 1.62ml/min/4500ml/min = 0.0011$$
5. A patient is admitted with an acute theophylline overdose. A serum level is measured at 45 μg/ml. Assuming an 8 hour half-life and no further drug absorption, how long does it take for the serum level to drop to the upper limit of the therapeutic range (20 μg/ml)?

\[ ke = \frac{0.693}{8\text{hr}} = 0.087\text{h}^{-1} \]

\[
\begin{align*}
20 &= 45 \cdot e^{-0.087 \cdot t} \\
\frac{20}{45} &= e^{-0.087 \cdot t} \\
\ln\left(\frac{20}{45}\right) &= -0.087 \cdot t \\
-0.811 &= -0.087 \cdot t \\
t &= 9.3\text{h}
\end{align*}
\]