1. Please mark the following questions with TRUE (T) or FALSE (F):

(T) (F) In general, in bioequivalence studies blood is collected for 3 or more terminal half lives.
(T) (F) In general, a multiple dose BE study for modified release dosage forms is not recommended.

Reduction of Regulatory Burden

(T) (F) Effect of body weight on volume of distribution depends on the lipophilicity of the drug.
(T) (F) For hydrophilic drugs, the volume of distribution usually correlates well with IBW.
(T) (F) The Cockroft-Gault equation dose not work well in children.

2. Given the data below for two Tylenol tablet formulations, are these products bioequivalent? What pharmacokinetic criteria did you use to draw this conclusion?

<table>
<thead>
<tr>
<th></th>
<th>Product A</th>
<th>Product B</th>
<th>Ratio (%) A/B</th>
<th>90% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC_{0-15 h} (g min/mL)</td>
<td>204.5</td>
<td>216</td>
<td>94.7</td>
<td>91.2-98.2</td>
</tr>
<tr>
<td>AUC_{0-\infty} (g min/mL)</td>
<td>212</td>
<td>222</td>
<td>95.5</td>
<td>88.6-102.4</td>
</tr>
<tr>
<td>C_{MAX} (ng/mL)</td>
<td>1020</td>
<td>1053</td>
<td>96.9</td>
<td>90.8-103.0</td>
</tr>
<tr>
<td>T_{MAX} (h)</td>
<td>44.6</td>
<td>52.8</td>
<td>84.5</td>
<td>71.3-100.2</td>
</tr>
<tr>
<td>T_{1/2} (min)</td>
<td>186.2</td>
<td>170.4</td>
<td>109.3</td>
<td>98.7-127.3</td>
</tr>
</tbody>
</table>

According to FDA’s guidance, bioequivalence is determined by the AUC_{0-\infty}, AUC_{0-\infty} and C_{MAX}. The 90% confidence limits of the RATIO of product A/Product B must fall within 80-125%. From this data, you would conclude that these two tablets are bioequivalent.

3. J.D. is a 25 years old male burger lover. He is 5’1” and weighs 80kg. His serum creatinine is normal with 1.2 mg/dl.

a. Please calculate his creatinine clearance and his volume of distribution for gentamicin.

IBW= 50 + (2.3)*(Height in inches > 60) + = 50 + 2.3 = 52.3 kg
Clinically obese: if TBW > 120% IBW
80 kg > 1.2*52.3 = 62.76 kg ➔ clinically obese ➔ use ABW
ABW = IBW + 0.4(TBW-IBW) = 52.3 + 0.4(80-52.3) = 63.38 kg
Cl_{Cr} = [(140-age)*(weight)] / (72*SCr) = [(140-25)*63.4]/ (72*1.2) = 84.4 ml/min = 5.06 L/h (use ABW)
Vd=0.25*63.4=15.9 L (use ABW)
b. Given 100% renal elimination, determine the $k_e$ and $t_{1/2}$ of gentamicin in this patient.

\[
k_e = \frac{CL}{Vd} = \frac{5.06}{15.9} = 0.318 \text{ h}^{-1} \quad t_{1/2} = \frac{0.693}{k_e} = 2.18 \text{h}
\]

if you use

\[
k_e = 0.00293 \times Cl_{cr} + 0.014 = 0.26 \text{ h}^{-1} \quad t_{1/2} = \frac{0.693}{k_e} = 2.67 \text{h}
\]

c. Design an IV dosing regimen (maintain dose and dosage interval) that will produce a steady state peak concentration of 10 mg/L and trough concentration of 1 mg/L.

\[
\tau = \frac{\ln \left( \frac{C_{\text{max}}}{C_{\text{min}}} \right)}{k_e} = \frac{\ln \left( \frac{10}{1} \right)}{0.318} = 7.2 \text{hr} \approx 8 \text{hr}
\]

\[
MD = Vd \times C_{\text{max}} \times \left( 1 - e^{-k_e \cdot \tau} \right) = 146.5 mg \approx 150 mg
\]

or use $k_e = 0.26$

\[
\tau = \frac{\ln \left( \frac{C_{\text{max}}}{C_{\text{min}}} \right)}{k_e} = \frac{\ln \left( \frac{10}{1} \right)}{0.26} = 8.85 \text{hr} \approx 8 \text{hr}
\]

\[
MD = Vd \times C_{\text{max}} \times \left( 1 - e^{-0.26 \cdot \tau} \right) = 139 mg \approx 150 mg
\]

4. Drug A has the following average pharmacokinetic parameters: CL 0.24 ml/min/kg, Vd 0.16 l/kg, fb 93%, Fren 49%. For a 70 kg, 50 yo male patient with a serum creatinine of 0.8 mg/dl, calculate the necessary intravenous daily dose to produce an average unbound serum concentration of 15 mg/l. How would you have to modify the dose, if the patient develops renal problems and his serum creatinine rises to 2.4 mg/dl?

\[
CL = 0.24 \times 70 = 16.8 \text{mL/min} = 1 \text{L/h}
\]

\[
V_d = 0.16 \times 70 = 11.2 \text{L}
\]

\[
CL_{R} = 0.49 \times 16.8 = 8.2 \text{ mL/min} = 0.49 \text{ L/h} \quad CL_{NR} = 0.51 \text{ L/h}
\]

\[
D = \frac{Cu \cdot CL \cdot \tau}{fu \cdot F} = \frac{15 \times 1.24}{0.07 \times 1} = 5.1 g
\]

new $CL_{R} = 0.33 \times 0.49 = 0.16 \text{ L/h}$

new $CL = 0.51 + 0.16 = 0.67 \text{ L/h}$

new dose $D = \frac{15 \times 0.67 \times 24}{0.07 \times 1} = 3.4 g$