1a. 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? **1 pt**

**AUC and Cmax**

1b. What is the lower and upper value of this interval?

**80-125% or 0.80 – 1.25**

2. An investigational new drug is eliminated entirely by liver (hepatic) metabolism, with a clearance of 1.40 L/min in subjects with an average liver blood flow of 1.50 L/min. Is it possible to calculate the drug’s approximate clearance in a congestive heart failure patient with a liver blood flow of 1.0 L/min but no change in hepatic extraction ratio? If yes, what’s the clearance, if no, explain why? **2 pts**

Yes it is possible.

We know that

\[ E = \frac{CL_i \cdot fu}{Q_H + CL_i \cdot fu} \]

\[ CL = Q_H \cdot E = Q_H \cdot \frac{CL_i \cdot fu}{Q_H + CL_i \cdot fu} \]

\[ 1.4 = 1.5 \cdot \frac{CL_i \cdot fu}{1.5 + CL_i \cdot fu} \]

Solving this we get

\[ CL_i \cdot fu = 21 \text{ L/min} \]

Now with new liver blood flow of 1 L/min …….. \[ Q_H (\text{new}) = 1 \text{ L/min} \]

\[ E_{(\text{new})} = \frac{CL_i \cdot fu}{Q_H (\text{new}) + CL_i \cdot fu} \]

\[ E_{(\text{new})} = \frac{21}{1 + 21} = 0.954 \]

\[ Cl_{\text{hep}} = 1 \cdot 0.954 = 0.954 \text{ L/min} \]

However with such a high extraction ratio, one could assume negligible change in its value with the decreased liver blood flow and assume it to remain same and may use the following method:

\[ Cl_{\text{hep}} = Q_H \cdot E \]

\[ E = Cl_{\text{hep}} / Q_H = 1.4 / 1.5 = 0.933 \]

For CHF patient: \[ Q_H = 1.1 \text{ L/min} \]

\[ Cl_{\text{hep}} = Q_H \cdot E = 1.0 \text{ L/min} \cdot 0.933 = 0.933 \text{ L/min} \]
Note that the change in E is practically negligible. So you could use the same E. But if you wanted to calculate the exact amounts one could calculate the change in E with change in liver blood flow. **Either of the answers will be accepted.**

3. Define the pharmacokinetic parameters $V_{dss}$ and $V_{darea}$ and explain, why $V_{dss}$ is always smaller than $V_{darea}$. **3 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 $\rightarrow V_{dss} < V_{darea}$**

4. A drug showed increase in tissue binding due a clinical condition. The pharmacist is of the opinion that the drug clearance remains the same but some other parameter changes. Is the pharmacist correct? Explain why? **2 pts**

**Yes, the pharmacist is right**

$V_d = V_B + \left( \frac{f_{u}}{f_{uT}} \right) * V_T$

With increase in tissue binding, $f_{uT}$ decreases and Vd increases
- Clearance and bioavailability are not changed
- Half-life is increased due to increase in Vd (decrease in $K_e$)

5. In general, what are the reasons an oral dosage form will have <100% bioavailability (List 3 reasons)? **1 pt**

- Solubility/dissolution rate
- Degradation
- P-glycoprotein
- Incomplete active transport
- First-pass effect
- Poor permeability
6. Chronic liver disease causes a 50% decrease in verapamil clearance. However, half-life of verapamil increases 4 fold in chronic liver disease. Clearly the volume of distribution has changed due to the chronic liver disease. What is the volume of distribution of verapamil in a patient with chronic liver disease? (Healthy population values: CL= 50L/h; VD= 300 L) 1 pt

Healthy CL = ke · Vd
50 = ke · 300 L
ke = 0.167 L/h
t1/2 = 4.15 h (or 4 hrs)
Hepatic CL 50% = 25 L/h
If t1/2 = 16.6 (or 16 -17 hrs)

Vd = CL/ke = 25 /(0.693/16.6) = 599 L ( 613 L)