PHA 5128 Dose Optimization II
Spring 2011
Case Study I Solution

If you have any questions regarding this case study, do not hesitate to contact Benjamin Weber (benjaminweber@ufl.edu) or your respective facilitator. Please remember that attendance is mandatory. 10 points will be deducted from your final score if you do not attend a case study without being officially excused by Dr. Derendorf.

Problem 1

A pharmaceutical company conducted a bioequivalence trial to receive market approval for their generic alternative to a brand name product. The statistician has obtained the following results. Based on the current FDA guideline for bioequivalence, would the products be considered as bioequivalent (assuming that all other requirements were met)? Explain why or why not?

Parameter	Test	Reference	T/R %	90% CI
AUC_{0-t}	1000	980	102.0	92.3 - 112.8
AUC_{inf}	2000	2010	99.5	90.1 - 110.0
C_{max}	19	18	105.6	95.6 - 117.7

Products would not be considered as bioequivalent. Extrapolated AUC is about 50% of total AUC. A new study needs to be conducted and plasma concentrations sampled for a longer time. It was a poorly designed study.

Problem 2

A 37-year-old man is hospitalized. The clinical pharmacists is ask to recommend a dosing regimen for drug A (Dose = 800 mg, CL = 50 L/h, VD = 200 L).The plasma-concentration-time profile of drug A is known to follow a one-compartment body model. For the following scenarios, calculate the peak and trough concentrations (for single dose trough concentration after 12 h).

a) Single Dose, IV bolus

$$C_{peak} = \frac{Dose}{VD} = \frac{800\ mg}{200\ L} = 4\frac{mg}{L}$$

$$C_{trough} = C_{peak} * e^{-k_e * t} = \frac{800\ mg}{200\ L} e^{-0.25h^{-1} * 12h} = 0.199\frac{mg}{L}$$

b) Single Dose, Short-term infusion, T = 2 h

$$C_{peak} = \frac{Dose}{CL * T}\left(1 - e^{-k_e * T}\right) = \frac{800mg}{50\frac{L}{h} * 2h}\left(1 - e^{-0.25h^{-1} * 2h}\right) = 3.15\frac{mg}{L}$$

$$C_{trough} = C_{peak} * e^{-k_e * t} = 3.15\frac{mg}{L} e^{-0.25h^{-1} * 10h} = 0.259\frac{mg}{L}$$

c) Multiple Dose (steady state), IV bolus, τ = 24 h

$$C_{peak} = \frac{Dose}{VD}\frac{1}{(1-e^{-k_e*\tau})} = \frac{800\,mg}{200\,L}\frac{1}{\left(1-e^{-0.25h^{-1}*24h}\right)} = 4.01\frac{mg}{L}$$

$$C_{trough} = C_{peak} * e^{-k_e*t} = 4.01\frac{mg}{L}e^{-0.25h^{-1}*24h} = 0.01\frac{mg}{L}$$

Problem 3

Drug B is administered via an IV bolus injection. Determine an appropriate dosing regimen of drug B to achieve desired steady state plasma concentrations of 10 mg/L for the peak (drawn 2 h after the injection) and approximately 3.5 mcg/mL for the trough. Assume that drug B's plasma-concentration-time profile follows a one-compartment body model. (CL = 15 L/h, VD = 100 L).

$$\tau = \frac{ln\left(C_{peak,desired}\right) - ln\left(C_{trough,desired}\right)}{k} + t^*$$

$$= \frac{1.05}{0.15}h + 2h = 9\ h\ (round\ down\ to\ 8\ h)$$

$$Dose = \frac{C_{peak,desired} * VD * \left(1-e^{-k_e*\tau}\right)}{e^{-k_e*t^*}} =$$

$$\frac{10\frac{mg}{L} * 100L * \left(1-e^{-0.15h^{-1}*8h}\right)}{e^{-0.15h^{-1}*2h}} = 943.3\ mg$$

Problem 4

TRUE (T) or FALSE (F)

Poorly water soluble drugs that show a high first-pass effect usually have a low oral bioavailability

T F

For antibiotics, the free concentration at the infection site is correlated to their pharmacodynamic effect because they usually show a high tissue protein binding

T **F**

For high extraction drugs, the total plasma concentration at steady state is independent of plasma protein binding

T F

For low extraction drugs, the total plasma concentration at steady state is independent of plasma protein binding

T **F**

For a given drug, an increase in volume of distribution does not affect the AUC

T F

The half-life of a drug is a function of its clearance and volume of distribution

T F

Problem 5

Define IND, NDA, and ANDA and, for each, briefly give an example for a situation in which a pharmaceutical company would file such an application

IND: Investigational New Drug Application, get approval to administer a new drug to human subjects or patients

NDA: New Drug Application, get market approval for a new drug, passing three stages of clinical trials required

ANDA: Abbreviated New Drug Application, get market approval for a generic alternative to a brand name product

Problem 6

Define bioavailability and bioequivalence

Bioavailability

Rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action

Bioequivalence

Absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study