2016 Non-Clinical Safety SAQs

1. There are general characteristics that distinguish MAbs and NCEs. In the following table put a few words in each column that summarize those differences for typical members of each class. (1 point per comparison)

Typical Characteristic	**NCE**	**MAb**
Molecular Weight		
Species specificity		
Immunogenicity Risk		
Half Life		
Routes of administration		
On or Off-target Toxicity		
Blood Brain Barrier permeability		
Routes of elimination		
Targets		
Manufacture		

2. List 5 different factors to consider when determining the starting dose for a NCE in a FTiH study using healthy volunteers. (2 marks per factor)

3. Outline the minimum package of GLP non-clinical safety studies required to support a SAD FTiH study in healthy vounteers for a NCE.
   (1 mark each)

   What would be the major differences in this package if the product was a MAb?

(2 marks)

a) Briefly describe the types of data/information that are needed from non-clinical studies to support a phase 1 first in human study for a New Chemical Entity (NCE) (8 marks)
b) List 4 additional types of non-clinical data that are (or maybe) needed to support a marketing authorization application for this NCE (2 marks)

2017– PK SAQs

Q1:.

Preclinical DMPK data for a new oral cardiovascular drug A predict the following to occur in human

- **40% renal clearance**
- **60% CYP metabolic clearance composed of**
    - **CYP3A4 - 30%**
    - **CYP2C19 - 30%**

a) **Outline a study design for a renal impairment study for this drug ? (3 marks)**
b) **is it necessary to perform a renal impairment study ? (1 marks)**
c) **What concerns does the CYP2C19 metabolism raise ? (2 marks)**
d) **outline a clinical study to determine if metabolism via CYP2C19 is clinically relevant ? (4 marks)**

Q2:). You are designing a clinical relative bioavailability cross-over study to transition from the current formulation to a new one for a drug with a short (24h) half-life

a) **What are the key PK parameters that you will use in the comparison of PK performance ? (2 marks)**

b) **Write the formula for relative bioavailability ? (2 marks)**

c) **What's the minimum washout period you would require between doses ? (1 mark)**
d) **The drug has a narrow therapeutic margin, how does this effect how you consider relative bioavailability ? (2 marks)**
e) **If the half-life was very long (4 weeks) how might you want to change the study design ? (2 marks)**
f) **How is absolute bioavailability different to relative bioavailability ? (1 mark)**

Q3: You are choosing between 2 drug candidates for a chronic disease. It is required to keep the trough blood level above a certain threshold to achieve activity

Drug A – short half-life (3h)

Drug B – long half-life (72h)

a) **Which drug would seem preferable from a dosing frequency aspect and why ? (2 marks)**
b) **Approximately how long would it take each drug to reach steady state ? (1 mark)**
c) **If you wanted to get drug B to steady state more quickly how could you achieve this ? (1 mark)**
d) **If drug B showed saturable metabolism how would this effect the steady state level ? (1 mark)**
e) **If drug B showed auto-induction of metabolism how would this effect the steady state level ? (1 mark)**

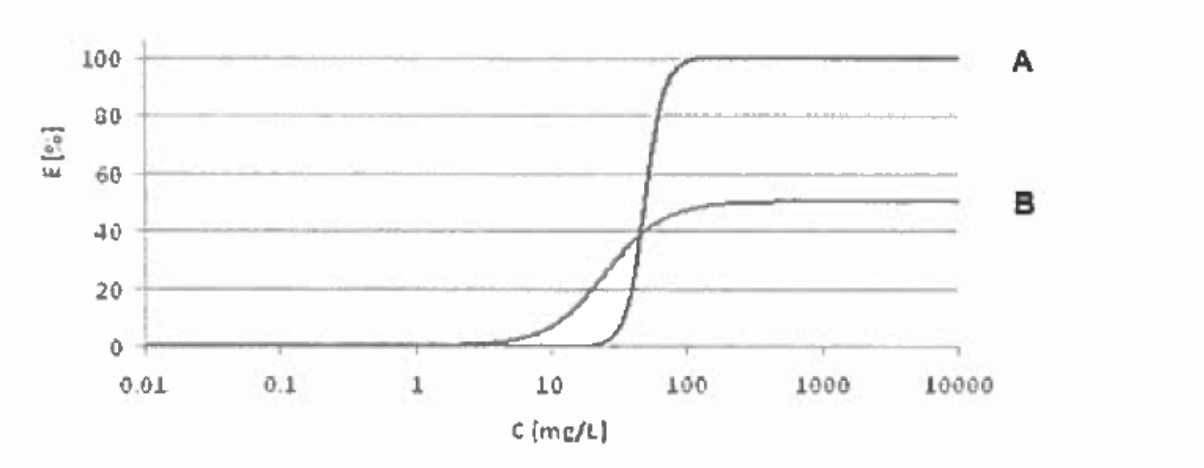
f) **How would you design a multiple dose volunteer PK study fo**

Q4

a. Define Oral Bioavailability (1)
b. List 4 factors that can influence the oral bioavailability of a drug (2)
c. Define elimination half-life (1)
d. Describe what is meant by Volume of Distribution (2)
e. Describe how elimination half-life is related to Volume of Distribution and Clearance. (2)
f. The mean steady state volume of distribution for a drug is 105L. What does this tell you about the drug? (2)

The graph below compares the concentration response for 2 different candidate molecules A and B the same receptor.

Y axis = receptor effect [E] vs. x axis = drug concentration [C]



a) Define the affinity of a molecule (1)
b) Define the Emax and EC50 (1)
c) Describe the data and conclusions that can be made regarding these agonist molecules A and B with respect to: (6)
    - Emax
    - EC50

    .

    - The slope of the concentration curves
d) With respect to efficacy and safety considerations, under what 2 conditions would you favour molecule A? (2)

2018 Non-clinical SAQs

a) List 4 methods for the non-clinical assessment of QT prolongation. (2 marks)

b) What information do these tests provide for clinical development? (3 marks)

c) Briefly describe the factors that influence the decision to continue clinical development when a positive signal for QT prolongation is seen in non-clinical testing. (5 marks)