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	*Less than 1000 Da*	*More than 100,000 Da*
Species specificity	*Not generally limited.*	*Often limited to primates only*
Immunogenicity Risk	*Low*	*High*
Half Life	*Short (hours)*	*Long (>10 days)*
Routes of administration	*All, oral, dermal, parenteral*	*Usually parenteral*
On or Off-target Toxicity	*Multiple mechanisms on or off target*	*On target only, extended pharmacology*
Blood Brain Barrier permeability	*Variable depending on phys chem and affinity for transporters*	*Low but not absent.*
Routes of elimination	*Metabolism, urinary biliary, respiratory*	*Catabolism*
Targets	*Intra or extracellular, all organ systems*	*Some protected systems (CNS, Inner ear, trans placental, testes) extra cellular only.*
Manufacture	*Chemical synthesis*	*Fermentation*

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)
    a. *The NOAEL in the most relevant safety species*
    b. *The body surface area correction factor/ Human Equivalent Dose*
    c. *A species sensitivity safety factor*
    d. *The relative potency of the molecule at the human target*
    e. *The Minimal Anticipated Biological Effect Level*

3. Outline the minimum package of GLP non-clinical safety studies required to support a SAD FTiH study in healthy vounteers for a NCE.
    a. *Ames test*
    b. *Mammalian cell mutation assay*

c. *Rodent general toxicity study*
d. *Non-rodent general toxicity study*
e. *hERG*
f. *Non rodent CV study*
g. *Respiratory study*
h. *Behavioral/CNS study*

(1 mark each)

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

i. *No mutagenicity or hERG studies*
j. *Non-rodent (primate) toxicology only, usually including the Safety Pharmacology endpoints*

(2 marks)

4

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)
   a. General toxicity data in rodent and non-rodent that determine NOAEL of sufficient margin to allow safe dosing. (2)
   b. Evidence that the NCE is non-genotoxic in bacterial and mammalian in vitro assays (2)
   c. Acute data demonstrating, in appropriate animal species that there are sufficient margins to CNS, respiratory, cardiovascular (non-rodent ECG) effects. AN in vitro assay for interaction with the hERG channel. (4)
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)
   a. Carcinogenicity bioassay in mouse and rat
   b. Reproductive toxicity studies (embryo-fetal development, fertility studies, pre and post-natal)
   c. Phototoxicity
   d. Immunotoxicity

(0.5 each)

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)**
   Single dose PK study, full plasma and urine PK profiles
   groups normal, mild moderate, severe renal impairment (minimum 8/group)
   PK parameters : Cmax, AUC, tmax, t1/2 endpoints, Ae in urine, CLr
   Statistical comparison of each impaired group v normal group
   Correlation of exposure (AUC, Cmax) with creatinine clearance

b) **is it necessary to perform a renal impairment study ? (1 marks)**
   yes,

c) **What concerns does the CYP2C19 metabolism raise ? (2 marks)**
   Polymorphism (lower expression in Asian subjects)
   Possible DDIs with CYP2C19 inhibitor
   CYP2C19 is polymorphic enzyme with different expression across ethnicities

d) **outline a clinical study to determine if metabolism via CYP2C19 is clinically relevant ? (4 marks)**
   healthy volunteers single dose PK study
   single dose drug A alone – PK assessed
   single dose drug A + CYP2C19 inhibitor eg fluconazole – PK assessed
   compare PK exposure of drug A in presence and absence of fluconazole

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)**
   Cmax, AUC, tmax,
b) **Write the formula for relative bioavailability ? (2 marks)**

$$F = \frac{F^A}{F^B} = \frac{AUC^A}{AUC^B} \times \frac{Dose^B}{Dose^A}$$

c) **What's the minimum washout period you would require between doses ? (1 mark)**
   120h (5x half-life)
d) **The drug has a narrow therapeutic margin, how does this effect how you consider relative bioavailability ? (2 marks)**
   Need to confirm that new formulation has very similar exposure (probably large size and narrow acceptance criteria)
e) **If the half-life was very long (4 weeks) how might you want to change the study design ? (2 marks)**
   Switch to parallel group design
f) **How is absolute bioavailability different to relative bioavailability ? (1 mark)**
   The reference is an IV dose, not another oral dose

$$F = \frac{AUC_{oral}}{AUC_{IV}} \times \frac{Dose^{IV}}{Dose^{PO}}$$

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)**
   Drug B. Likely given 1/day and far less frequent per day than drug A
b) **Approximately how long would it take each drug to reach steady state ? (1 mark)**
   A – 15h , B 360h
c) **If you wanted to get drug B to steady state more quickly how could you achieve this ? (1 mark)**
   Give a loading dose on day 1 or give 2 doses on day 1
d) **If drug B showed saturable metabolism how would this effect the steady state level ? (1 mark)**

Would increase steady state level

e) If drug B showed auto-induction of metabolism how would this effect the steady state level ? (1 mark)

Would decrease steady state level

f) How would you design a multiple dose volunteer PK study for drug B ? (4 marks)

Single dose, PK assessed for 1 week (maybe longer)

assess PK (cmax, tmax, AUC, T1/2)

washout 1 week after first dose

Multiple once daily dosing for 3 weeks (maybe longer)

assess PK Cmax, tmax, AUC, AUCtau, accumulation ratio,

repeat at additional doses

assess dose proportionality for day 1 and end of multiple dosing exposures

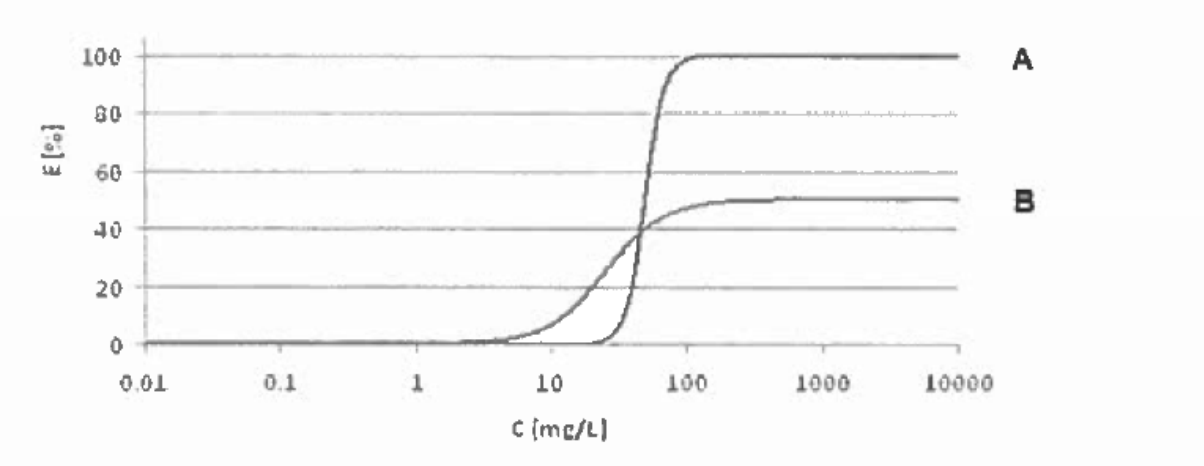
assess time dependency of kinetics from day 1 to end of multiple dosing

Q4

a. Define Oral Bioavailability (1)
    a) (F%) is the fraction of an oral administered drug that reaches systemic circulation.
b. List 4 factors that can influence the oral bioavailability of a drug (2)
    a) Absorbtion, dissolution, metabolism, excretion, Pgp,
c. Define elimination half-life (1)
    a) The time required for the concentration of the drug to reach half of its original value (after the distribution phase)
d. Describe what is meant by Volume of Distribution (2)
    a) The apparent volume in which a drug is distributed. The theoretical volume that would be necessary to contain the total amount of an administered drug at the same concentration that it is observed in the blood plasma.
e. Describe how elimination half-life is related to Volume of Distribution and Clearance. (2)
    a) The half-life is proportional to the Vd, and inversely proportional to the Cl.
f. The mean steady state volume of distribution for a drug is 105L. What does this tell you about the drug? (2)
    a) It is highly distributed into tissue. It is probably non-polar/lipophilic and diffused into the body fat.

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)

The relationship between molecule concentration and binding to its target. High-affinity binding implies that relatively low concentrations of a molecule are required to maximally occupy a ligand-binding site and trigger a physiological response.

b) Define the Emax and EC50 (1)

Emax is the maximum response achieved from a molecule (note: Intrinsic activity is the response relative to the maximum achievable or compared to the most potent molecule).

EC50 is the concentration that produced the half maximal response for a molecule.

c) Describe the data and conclusions that can be made regarding these agonist molecules A and B with respect to: (6)

- Emax

  As the Emax for A and B are achieved at approximately the same concentration, but the Emax of B is only 50% of that of A. A is a full agonist. B is a partial agonist.

- EC50

  Compound B has the lower EC50 and on this basis, would be considered more potent. EC50 would normally be expressed in molar equivalents rather than mg/L.

- The slope of the concentration curves

The responsive curve for compound A is much steeper around the EC50 than compound B. So smaller changes in concentration around this value elicit much larger concentration dependent effects. The plateau of A and B has been achieved at similar concentrations. If they have similar molecular weights then binding affinity is similar.

d) With respect to efficacy and safety considerations, under what 2 conditions would you favour molecule A? (2)

Where full agonism is required. Where there is an acceptable safety margin between Emax and the NOAEL.

2018 Non-clinical SAQs

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

1. hERG blockade by patch clamp
2. ECG in non-rodent
3. Rabbit Ventricular Wedge preparation assessment
4. Structure-Activity assessment of the candidate molecule

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

The **margin** between the intended **free Cmax** of the molecule and the **inhibitory concentration profile (IC50)** of the hERG channel. Together with in vivo **impact on QT interval** an assessment of the **potential risk for TdP** can be determined.

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)

a. Margin to the effect
b. Risk-benefit
c. Mechanism of prolongation
d. Co-administration with other QT prolonging agents
e. Exacerbation by DDI