

**Question 4:**

4. With respect to the evaluation of the cardiac safety of new drugs;
- a) What is the QT interval on the ECG and what does it represent? (1 mark)
  - b) List the non-clinical studies by which the QT/QTc prolongation potential of a new drug is evaluated. (1 mark)
  - c) Summarise when and how the QT/QTc prolongation potential is evaluated in the clinical development of a new active substance. (8 marks)

***Please note that the exam responses have been transcribed verbatim and may not be correct. These examples are provided to for informational purposes only. The FPM will not enter into any correspondence about them.***

**Question 4 (example of a good response)**

a) QT interval is time period from the start of the Q wave to the end of the T wave.

Annotated diagram of QRS complex correctly drawn by candidate with the following text beside it: Diagram

Corrected QT = QTc

Corrected for heart rate

Formulae Bazett's or Fridericia's (preferred)

[QT interval] Represents cardiac depolarization. Surrogate for Torsades de pointes

b) Non-clinical studies: hERG in vitro potassium channel assessment of inhibition

CVS safety study in rodent and non-rodent eg dog with cardiac telemetry.

Isolated non-rodent (dog or rabbit) Purkinje fibre conduction study (optional).

c) QT / QTc potential evaluation clin. development when:

Phase I healthy volunteer studies – intensive ECG monitoring with 12 lead ECG and Holter telemetry.

Thorough QT / QTc study to assess risk and decide if further monitoring is required later in development or if the compound should be withdrawn from development.

Usually a single dose placebo and active control (moxifloxacin) study with at least 2 doses of the investigational medicine.

## Sample SAQ responses from 2010 Diploma in Pharmaceutical Medicine examination

2 period, 2 sequence crossover design, unless long  $\frac{1}{2}$  life. If so, need parallel group design.

Multiple ECGs collected pre-dose and at time intervals post-dose.

Subjects must have QT / QTc < 450 msec for inclusion and no family history of long QT syndrome, unexplained syncope or unexplained sudden death suggestive of long QT.

Analysis: positive control must have 95% confidence interval > 0 through point estimate approx 5msec to demonstrate assay sensitivity.

For the IMP: upper bound of 95% CI < 5 msec suggests no concern  
>5 msec - <10 msec suggests caution  
>10 msec – drug may have potential to prolong QT / QTc and represent a risk of dysrhythmia.

If IMP continues development – need further evaluation in Phase II / III through ECG monitoring if thorough QT study has suggested prolongation.

### Question 4 (example of a poor response)

a) QT interval – on ECG – from start of Q to end of T wave

Annotated diagram of QRS complex drawn by candidate  
QT interval represents repolarisation.

b) in vitro hERG assay

in vivo telemetry e.g. dog

in vitro Purkinje fibre assay

c) - When? In vitro hERG and dog telemetry done as part of core safety battery prior to 1<sup>st</sup> in man.

- Specific QT / QTc Purkinje fibre assay done prior to Marketing Authorisation Application. According to ICH, only required in systemically absorbed products.
- How

hERG – cells expressing hERG (HEK 273) exposed to drug with and without post mitochondrial fraction patch clamp testing of potentials.

Telemetry – often performed in dog. Dog exposed to test substance. 24 hour ambulatory monitoring

Purkinje fibres – exposed to test substance. Contraction induced with subsequent measurement of repolarisation time and potentials.

**Sample exam question responses 2010 Dip Pharm Med**

Question 10

10. a) List the minimum information required for an adverse event report to be valid. (2 marks)
- b) You are responsible for the pharmacovigilance activities relating to a flu vaccine. Three fatal seizures have been reported within three weeks of launch of the vaccine. What do you need to know in order to evaluate these cases fully? (8 marks)

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**Question 10 (example of an excellent response )**

a)

Identifiable patient  
Identifiable reporter  
A suspect drug  
An adverse event

b)

Is there sufficient data to meet Bradford-Hill or other causality criteria to establish a causal relationship between the flu vaccine and the fatal; seizures; and does this alter the benefit:risk balance of the product warranting action, such as labelling change, urgent safety restrictions, suspension/recall or withdrawal? To further evaluate this signal:

i) Case-level data:

Full medical details: sequence of events, contributing or confounding factors, medical and family history, events around the time of the seizure (eg. Electrolytes, CT scans, EEG), concomitant medication.

Confirmation of date, dose, batch of vaccine received.

Is there a possible product quality complaint? Eg contamination

ii) Review existing data:

Could include pre-clinical, clinical database and post-marketing data. Is there suggestion of either an increased risk or biological mechanism for the seizures? Is there a disproportionality signal emanating either from the internal company database or when comparing external data such as WHO Vigibase or FDA VAdees?

Is an appropriate SMQ available to retrieve all relevant cases from the safety database for ad hoc analysis?

iii) Epidemiology:

## Sample SAQ responses from 2010 Diploma in Pharmaceutical Medicine examination

What is the background rate of fatal seizures in the population receiving the vaccine, and those who suffered the fatal seizure?

What is the exposure estimation for the vaccine in the three weeks since launch? This will provide a rough estimate for the denominator to make a guesstimate at frequency.

Bradford-Hill criteria

Analogy

Coherence

Seen in other vaccines?

Consistency

Temporality

Occurred after administration

Specificity

How many seizures occurred w/o vaccine

Plausibility

What is the mechanism?

Experimental evidence

Pre-clinical data?

Dose-response relationship

(probably standard dose)

Strength of association

To complete pharmacovigilance activity, and once the level of risk has been quantified, the level of benefit also needs to be considered in order to make a benefit:risk assessment. In this scenario, use of a vaccine, probably in a healthy subject, is unlikely to provide sufficient benefit to offset significant risk.

### Question 10 (example of a poor response)

a) For an AE report to be valid it should have

- Information regarding exposure to medicinal product
- Onset / duration / cessation (whether ongoing)
- Any temporal causality to IMP whether suspected or not suspected
- Any grades of severity (mild / moderate / severe attached)

b) 3 reported seizures (fatal) within 3 weeks of launch of a vaccine is a matter of utmost clinical significance. Being responsible for pharmacovigilance activity relating to this newly launched vaccine, I need to explore the situation very carefully with utmost diligence and attention to detail. I shall require

- Full clinically relevant all the case reports of these "3" reported seizures
- I shall analyse if these were pre-existing medical conditions
- Any pre-clinical data to suggest whether the flu vaccine has potential to cause seizures
- All blood samples, if done at the time of hospitalization
- Full case reports
- I shall report the findings to the regulatory authorities in 14 days
- Add / improve into the product literature
- Advice to do further studies
- I'll need all trial documents regarding safety/ AEs to analyse and submit my report.