1177

Ollscoil na hÉireann, Gaillimh
National University of Ireland, Galway

Summer Examinations 2004 / 2005

Exam Code(s)	4BS2
Exam(s)	
Module Code(s)	PM415
Module(s)	
Paper No.	5
Repeat Paper	
External Examiner(s)	Professor Iain Campbell
Internal Examiner(s)	Dr. John Kelly
	Dr. Maura Grealy
Instructions:	Answer ALL Questions
Duration	3 Hours
No. of Pages	1
Department(s)	Pharmacology
Course Co-ordinator(s)	Dr. John Kelly

Requirements:

MCQ	
Handout	
Statistical Tables	
Graph Paper	
Log Graph Paper	
Other Material	YES

1. You are provided with a recently published research paper. Provide this paper with a title and write a 200-word abstract which includes an introduction, methods and discussion section. **(50 marks)**

2. What are the "3 Rs". Make a list of possible initiatives that could be introduced whereby the principles of the "3 Rs" can be applied to the preclinical safety evaluation of a drug. **(7.5 marks)**

3. A commercially available chemical is to be introduced into your laboratory as a reference positive control in an *in vitro* assay investigating novel anticancer drugs. Outline the safety measures that would need to be considered and implemented before introducing this chemical. **(7.5 marks)**

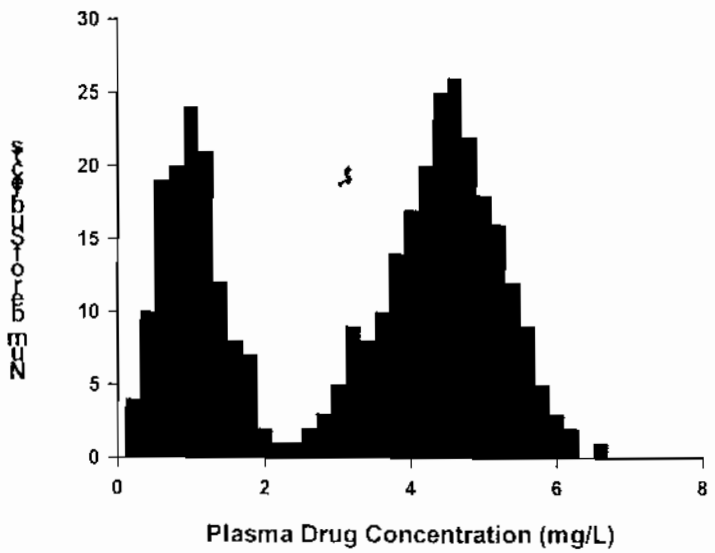
4. A Drug Company examined the pharmacokinetic profile of three biopharmaceuticals. Ideally, they were looking for a compound with a 24 hour half-life and high oral bioavailability. The following data were obtained following a single oral administration to human volunteers:

Parameter	**C12,356**	**C12,357**	**C12,358**
Total clearance (L/hour)	97	3	12
Volume of distribution (L)	250	25	420
Fraction excreted unchanged	0.1	0.1	0.8

Assume that the liver blood flow is 90 L/hour.

Which of the three drugs would you recommend for further evaluation? Give reasons for your choice

A subsequent investigation of the plasma concentration of the selected drug produced the following profile:



Describe the profile and the implications for the further development of this compound. **(10 marks)**

5. Five chemical structures have been identified as being potentially useful to develop a new antidepressant which would selectively inhibit serotonin and noradrenaline reuptake but be devoid of the adverse effects associated with tricylic antidepressants. Below are the results obtained for the affinities of a representative chemical from each drug class for transporters and certain receptors:

Drug Class	**SERT**	**NART**	**α_1**	**Muscarinic**	**H_1**
A	2.0±0.4	1.8±0.3	127.1±9.6	262.4±13.3	140.1±8.5
B	15.5±1.5	241.2±52.1	>1000	>1000	>1000
C	2.3±0.5	2.0±0.2	719.2±61.1	905.1±87.6	920.5±87.5
D	1.7±0.3	3.5±0.4	68.1±7.1	31.3±3.3	7.5±0.9
E	158.2±22.2	471.3±58.1	45.2±6.7	15.7±1.3	8.7±0.7
Amitriptyline	3.5±0.3	2.7±0.3	122.1±8.6	238.4±15.3	125.4±9.5

Data are expressed as mean + S.E.M. Ki (nM) of at least 3 separate experiments, each performed in triplicate. SERT: serotonin reuptake transporter; NART: noradrenaline reuptake transporter;

From this information, which structure would you select for further investigation? Give reasons for your answer. **(10 marks)**

6. You have been asked to investigate the effects of a drug on noradrenaline levels in zebrafish embryos cultured in 4-well plates. Outline five important factors you would take into consideration in designing this experiment. (One sentence each). **(5 marks)**

7. List 5 requirements for proper assay validation. Briefly detail how you would test assay performance under each of these headings. **(10 marks)**