A. 5 Pharmaceutical aspects

a. Define shelf life and outline factors that may influence drug potency during storage.

The period over which a drug loses 10% of its potency or its guarantee of sterility when stored according to the manufacturer's specifications.

b. Describe methods of preserving shelf-life of drugs

Suitable method depends on the nature of the reactions which would degrade the drug.

physical
- sealed containers
- temperature
  - refrigeration or freezing to reduce the rate of degrading reactions
  - e.g. sux, atracurium, blood products
- light
  - dark or opaque containers minimize light-induced changes
  - e.g. halothane, nitroprusside
- drying
  - dried to powder to reduce reaction rates
  - e.g. thio, vec, many antibiotics

chemical
- controlled pH
  - many drugs in solution have NaOH or HCl and buffer added
- reducing or oxidizing agents in solution
  - usually reducing agents, may cause reactions (e.g. sulfites, nitrites)
- reaction with or adsorption to a carrier
  - sugar glasses in phase IIb trials for α_1-antitrypsin
- controlled atmosphere (N_2) or vacuum
  - thio, some antibiotics

microbiological
- pretreatment to sterilize drug
  - heat, radiation, ethylene oxide
- risk of contamination minimized by physical and chemical methods which remove water (and oxygen)
- anti-microbials
  - added to many oral agents
  - e.g. alcohol, benzalkonium chloride

c. Describe the mechanisms of action and potential toxic effects of buffers, anti-oxidants, anti-microbials and solubilizing agents added to drugs.

additives
- buffers
  - commonly NaOH, KOH, HCl used to control pH
  - carbonate buffers in LA solutions, methohexitone, thio…
  - phosphate buffers
  - benzenesulfonic acid in atracurium
- osmolal agents
  - mannitol in dantrolene, vecuronium
  - glucose in spinal LA solutions
- stabilizing agents
  - antioxidants
    - Na metabisulphite in catecholamine solutions: neurotoxicity

- other agents
  - thymol in halothane prevents light inactivation
  - N_2 atmosphere in thiopentone
- antimicrobials
  - methylparabens used in multidose vials, cause hypersensitivity
  - methyl- and propyl-hydroxybenzoate in topical and IV solutions
  - benzalkonium chloride in nebulizer solutions
  - benzyl alcohol in some water preparations
- solubilizing agents
  - lipid solutions
    - Cremaphor EL: polyoxyethylated castor oil, hypersensitivity
    - Intralipid: soybean oil, egg phospholipid, glycerol
      - high omega-6-fa content
    - propylene glycol & alcohols solution e.g. diazepam
    - polyethylene glycol in temazepam gelcaps (phlebitis if injected)
- propellants
  - chlorofluorocarbons in inhalers may be replaced with other agents e.g. N_2
- pharmacokinetic alteration
  - binding agents: protamine in insulin
  - uptake: adrenaline in LA
- compliance
  - flavouring, colouring etc.

d. Outline the variations in generic nomenclature of commonly used drugs.

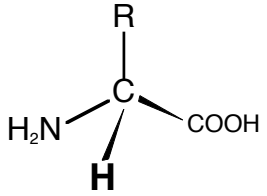
Not approved	Approved name	Not approved	Approved name
acetaminophen	**paracetamol**	laevulose	fructose
albuterol	**salbutamol**	levarterenol	noradrenaline
aminoacetic acid	glycine	levothyroxine	thyroxine
aminoacridine	aminacrine	**lidocaine**	**lignocaine**
amobarbital	amylobarbitone	**meperidine**	**pethidine**
aneurine	thiamine	mephobarbital	methylphenobarbitone
anthralin	dithranol	methenamine	hexamine
asparaginase	colaspase	niacin	nicotinic acid
azidothymidine	zidovudine	**nitroglycerine**	**glyceryl trinitrate**
calciferol	ergocalciferol	norephedrine	phenylpropanolamine
carvomenthenol	terpineol	**norepinephrine**	**noradrenaline**
chlormethin	mustine	norethinderone	norethisterone
cortisol	hydrocortisone	omadine	pyrithione
cromolyn	cromoglycate	penicillin G	benzylpenicillin
dextrose	glucose	penicillin V	phenoxymethylpenicillin
dibucaine	**cinchocaine**	phytonadione	phytomenadione
epinephrine	**adrenaline**	pizotyline	pizotifen
ergonovine	**ergometrine**	propoxyphene	dextropropoxyphene
furosemide	**frusemide**	pyrilamine	mepyramine
glyburide	**glibenclamide**	**tetracaine**	**amethocaine**
hexamurium	distigmine	trolamine	triethanolamine
isoprotenerol	**isoprenaline**	tromethamine	trometamol

e. Define isomerism, provide a classification with examples and explain its significance.

Isomers are molecules having the same empirical formula but different structures. Chemical isomers have completely different atom to atom bonds, for example enflurane and isoflurane or edrophonium and ephedrine HCl. Stereoisomers or enantiomers have the

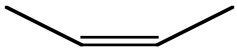
same bond arrangements but differ in three-dimensional structure due to the presence of chiral centres (atoms bonded to four different groups) which may exist in two mirror-image arrangements or bonds without rotational freedom such as unsaturated carbon-carbon bonds with the two carbon atoms each bonded to different groups.

Chiral centres are present in all amino-acids and many other organic compounds including sugars. They are usually designed D- or L- or d- or l- or R- or S- or (+) or (-) isomers according to their configuration or effect on the polarization of light. Unsaturated bonds are present in many lipids and other molecules and are designated cis- or trans- isomers (Z- or E-) according to whether the major functional groups on the carbon atoms involved are on the same or opposite sides.



a chiral carbon


trans-


cis-

Many organic compounds include multiple chiral centres (e.g. atracurium) or unsaturated bonds (e.g. retinoic acid), yielding multiple optical isomers. As the isomers are different in three dimensional structure, they often bind with different affinities to receptor sites with specific three-dimensional structure and are degraded by enzymes at different rates.

Examples (optical isomers)
- isomers equally active
- isomers have slightly different potencies and metabolism, e.g. atracurium, ropivacaine
- isomers have different actions, e.g. quinine/quinidine
- one isomer is active and drug is administered as a racemic mix, e.g. verapamil
  - makes blood levels misleading (active L-verapamil is cleared more rapidly)
- one isomer is active and is administered alone, e.g. l-DOPA

f. Describe the process by which new drugs are approved for research and clinical use in Australia and outline the phases of human drug trials.

Safety tests in animals/tissue culture
- acute toxicity
  - LD_{50} in animals (2 species, 2 routes), “no effect” dose
- subacute toxicity
  - up to 6 months use in three dose ranges in 2 species
- chronic toxicity
  - 1-2 years if prolonged use is planned in humans
- specific testing
  - reproduction, carcinogenesis, mutagenicity (Ames test), investigative toxicology

Human evaluation
- phase I
  - establish dose-effect relationship in healthy volunteers or diseases volunteers not blinded, establishes predictable adverse effects and pharmacokinetics
- phase II
  - small single-blind trials in diseased patients with placebo and positive controls
- phase III
  - large, usually multicentre, double-blind or crossover trials
- phase IV
  - on-going surveillance for adverse effects during marketing

Phases I trials often start more than 4 years after initial synthesis and phase III may

not be completed until 8 years after initial synthesis. Some drugs are made available for life-threatening or serious diseases without completion of phase III or even phase II trials, e.g. some antiretrovirals.

Australian approval is distinct from overseas approval and applies similar criteria of safety and efficacy as in the US and UK. PBS listing and approval for hospital pharmacopoeia availability depends on cost-effectiveness as well.

The detection of rare adverse effects requires more subjects than are available in phase III trials. For example, to detect the doubling in incidence of a 1/1000 adverse effect requires 18000 subjects (ß=0.20, α=0.05). Thus most rare or unpredictable adverse effects will not be detected prior to marketing.

List the plants from which commonly used drugs are derived.

Claviceps purpurea	ergotamine
Erythroxylon coca	cocaine
Papavertum somniferum	morphine, codeine, thebaine, papaverine etc.
Digitalis purpurea, lantana	digoxin
Rauwolfia serpentina	reserpine
Atropa belladonna	atropine
Hyocyamus niger	hyoscine