Which one of the following definitions best defines the term ‘pharmacovigilance’?

a. Monitoring patients during pre-clinical and clinical trials for the development of serious adverse effects to medicines
b. Monitoring the safety of medicines in clinical use and taking appropriate action to minimise the risk to patients
c. Monitoring the effectiveness of medicines in clinical use and taking appropriate action to minimise the risk to patients
d. Monitoring patients during clinical trials to determine whether the medicine they are taking interacts with any of their current medicines
e. The act of licensing a new drug and making it available for clinical use

Answer b. The activity of monitoring the safety of medicines in clinical use and taking appropriate action to minimise risk is known as pharmacovigilance, and is governed by a range of complex UK and European regulations.

Which one of the following procedures is not a type of licensing procedure used to license a new medicine for human use in the European Union?

a. National
b. International
c. Centralised
d. Decentralised
e. Mutual recognition

Answer b. There are four types of licensing procedure in the European Union (EU), depending on the indication and nature of the active ingredient of the medicine and whether the product is to be marketed in one or more member states:
- The centralised procedure is mandatory for certain classes of therapies, biotechnological products, new active substances for certain diseases (cancer, HIV/AIDS, diabetes, autoimmune, neurodegenerative, and viral diseases) and orphan medicines.
- The decentralised procedure involves an application for a marketing authorisation being submitted simultaneously to a number of member states, one of which takes the lead, via its ‘competent authority’ in assessing the drug.
- The mutual recognition procedure is used where an applicant has an existing authorisation in one member state and applies for authorisation in other member states. In such cases, the other member states’ ‘competent authorities’ use the assessment of the medicinal product by the original single member state as a basis for their own evaluation and national decision.
- The national procedure can be used when an application is sought in one member state.

In the UK, drugs that are deemed to require more intensive monitoring (usually new drugs) are denoted by a black triangle symbol (▲). Which one of the following is not a reason for assigning a black triangle:

a. addition of a black triangle by another EU member state
b. the product contains a new combination of active substances
c. administration of the drug via a new route of administration or drug delivery system
d. a significant new indication which may alter the established risk/benefit profile of that drug
e. an established medicine which is to be used in a new patient population

Answer a. This non-statutory, voluntary scheme, which is operated by the Medicines and Healthcare products Regulatory Agency (MHRA), encourages reporting of all (serious and non-serious) adverse effects suspected to be associated with a drug identified by a black triangle. The reasons for assigning a black triangle:
- the drug is an active substance which has been newly licensed for use in the UK;
- it contains a new combination of active substances;
- administration of the drug via a new route of administration or drug delivery system;
- a significant new indication which may alter the established risk/benefit profile of that drug;
- an established medicine which is to be used in a new patient population.
Answer d. Key changes that affect the UK include the following:

- The scope of reporting via Yellow Cards will be extended to include medication errors and occupational exposure and adverse effects from the use of a medicine outside the terms of the marketing authorisation, including overdose, misuse, abuse of the product and medication errors.
- The voluntary black triangle scheme in the UK will be replaced by an EU-wide mandatory ‘additional monitoring scheme’ (all suspected adverse effects to be reported).
- The MHRA is required to have a web portal (linked to a portal at the EMA) which will give access to all public assessment reports, SPCs and patient information for all UK medicines (expected to be completed in 2013).
- The EU database (Eudravigilance) will become the definitive database on adverse effects in the EU. It will contain all reports received by national authorities and companies making information on all ADRs centralised in one place in the EU. The MHRA will still retain a national database and it is crucial that healthcare professionals and patients continue to report suspected adverse reactions through the Yellow Card scheme.

Responsibility for the safety of products authorised in the UK only will remain with the UK licensing authority.

The changes to the European law affecting pharmacovigilance had to be implemented by the UK government by July 2012.

Which one of the following statements about the changes resulting from the European law affecting pharmacovigilance legislation is correct?

a. The Eudravigilance database will no longer provide the level of information required and will be replaced by a web portal developed by the MHRA

b. Responsibility for the safety of products authorised in the UK only will now be taken over by the European Medicines Agency

c. The voluntary black triangle scheme in the UK will continue in its current form

d. The scope of reporting via the Yellow Card scheme will be extended to include medication errors, occupational exposure and adverse effects associated with a medicine’s use outside the terms of its marketing authorisation

e. The changes to the European law affecting pharmacovigilance are due to be implemented in the UK by July 2014

Question 5

Which one of the following statements is correct?

a. Drug Safety Update is a monthly publication produced by the European Medicines Agency

b. Pharmaceutical companies are legally obliged to pass on reports of serious adverse reactions within 15 days

c. The Yellow Card scheme operated by the Medicines and Healthcare products Regulatory Agency does not allow reporting of adverse events relating to over-the-counter products

d. Regulatory action related to the adverse effects of the antidepressant drug citalopram on the heart occurred in the UK several months before the USA

e. Summary of product characteristics (SPC) for all licensed products are now available on a single website

Answer b. The MHRA publishes significant new safety warnings in its monthly publication, Drug Safety Update. The Yellow Card scheme enables healthcare professionals and the public to report to the MHRA suspected adverse effects related to prescribed or over-the-counter medicines, herbal medicines, certain blood products, vaccines, medical devices, cosmetic treatments and unlicensed drugs. Regulatory action related to the adverse effects of the antidepressant drug citalopram on the heart occurred in the USA several months before the UK. It is still the case that an SPC for every product available in the UK is not available in one database.

Complete this module online

This CME/CPD module is available for completion online via BMJ Learning (learning.bmj.com) by subscribers to the online version of DTB. If you would like to add online access to your current subscription, please contact our Customer Services team on +44 (0)20 7383 6270 or email support@bmjgroup.com. As well as allowing you to complete CME/CPD modules online, an online subscription also gives you unlimited access to the entire DTB archive back to volume 1, issue 1.

For further information, please visit www.dtb.bmj.com
Mrs SK is a 38-year-old woman who was diagnosed with multiple sclerosis (MS) 2 years ago. For the last 6 months, she has experienced spasticity in her legs which has not responded adequately to drug treatment. What is the lifetime risk of developing MS in the UK?

a. 1 in 1,000  
b. 1 in 6,000  
c. 1 in 10,000  
d. 1 in 60,000  
e. 1 in 100,000

Answer a. Multiple sclerosis (MS) is a neurological condition that is estimated to affect around 60,000 people in England and Wales, with a lifetime risk in the UK of 1 in 1,000.

What proportion of people with MS are thought to have muscle spasticity at some point?

a. 30%  
b. 40%  
c. 50%  
d. 60%  
e. 70%

Answer d. About 60% of people with MS have muscle spasticity at some point.

What are the principal extracts from the cannabis plant present in the licensed preparation Sativex?

a. delta9-tetrahydrocannabinol and cannabidiol  
b. Tetrahydrocannabivarin and cannabidiol  
c. delta9-tetrahydrocannabinol and cannabigerol  
d. Tetrahydrocannabivarin and cannabigerol  
e. delta9-tetrahydrocannabinol and cannabichromene

Answer a. delta9-tetrahydrocannabinol and cannabidiol are the principal extracts from the cannabis plant present in a licensed preparation.
Question 4
Which one of the following statements correctly describes the Sativex studies?

a. Only one of the trials compared cannabis extract with an active comparator
b. One meta-analysis of 666 patients reported a statistically significant difference in favour of cannabis extract compared with placebo on individual endpoint analysis

c. One meta-analysis of 666 patients reported a statistically significant difference in favour of placebo compared with cannabis extract on individual endpoint analysis

Answer b. None of the trials had an active comparator to cannabis extract. One meta-analysis of 666 patients showed that there was a statistically significant difference in favour of cannabis extract compared with placebo on individual endpoint analysis; adjusted mean change from baseline of the rating scale used (either 100 mm visual analogue scale or 1–10 numerical rating scale) was −0.32 (95% CI −0.6 to −0.04, p=0.026).

In the 12-week phase of the ‘enriched design’ randomised placebo-controlled trial, the mean spasticity score reduced by a further 0.04 points in the treatment group, and increased by 0.81 in the placebo group, giving a mean treatment difference of 0.84 (95% CI −1.29 to −0.40, p=0.0002).

The SPC recommends that the dose should not exceed 12 actuations (sprays) per day; however, only one of the trials limited the treatment given to the licensed dose with no comment made about the average number of sprays used in the trials that permitted doses of the preparation that exceeded the licensed dose.

Question 5
Which one of the following adverse effects has not been reported with Sativex?

a. Dizziness and fatigue
b. Feeling ‘drunk’ or abnormal
c. Euphoria and disorientation
d. Seizures
e. Suicidal ideation

Answer d. The SPC states that from the clinical trials, very common unwanted effects (occurring in more than 1 in 10 patients) were dizziness and fatigue. Common unwanted effects (occurring in between 1 in 100 and 1 in 10 patients) include appetite changes, depression, disorientation, euphoria, amnesia, balance disorder, memory impairment, dysarthria, attention disorder, blurred vision, vertigo, constipation, diarrhoea, mouth ulcers, nausea vomiting, application-site pain, feeling drunk and feeling “abnormal”. Uncommon unwanted effects (occurring in between 1 in 1000 and 1 in 100 patients) include pharyngitis, hallucinations, illusions, paranoia, syncope, palpitations, tachycardia, hypertension, throat irritation, upper abdominal pain, tooth discoloration and application-site irritation.

According to the SPC, psychiatric symptoms such as anxiety, illusions, changes in mood, paranoid ideas and “in a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out”. The SPC states that these are “likely to be the result of transient CNS effects and are generally mild to moderate in severity and well tolerated”, but in the event of suicidal ideation, the SPC advises that the product should be stopped immediately and the patient monitored until the symptom has completely resolved.

Complete this module online
This CME/CPD module is available for completion online via BMJ Learning (learning.bmj.com) by subscribers to the online version of DTB.

If you would like to add online access to your current subscription, please contact our Customer Services team on +44 (0)20 7383 6270 or email support@bmjgroup.com. As well as allowing you to complete CME/CPD modules online, an online subscription also gives you unlimited access to the entire DTB archive back to volume 1, issue 1.

For further information, please visit www.dtb.bmj.com