Contribution of Yellow Cards to identifying safety issues

The value of the Yellow Card Scheme has been demonstrated many times and it has helped to identify numerous important safety issues, many of which were not recognised as being related to a particular medicine until we received information on Yellow Cards. After the table of safety issues there are some detailed case study examples.

Stay up to date with the latest emerging safety advice on medicines by subscribing to the MHRA's monthly bulletin called Drug Safety Update (DSU): www.gov.uk/drug-safety-update

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Table of safety issues to which Yellow Cards have contributed to

The following table shows some of the safety issues which Yellow Card reports have contributed to or helped identify:

Year	Medicine	Adverse Reaction	Resulting action or advice
September 2016	Posaconazole (Noxafil)	Tablets and oral suspension are not directly interchangeable	Strengthened product information warnings to clarify the oral solution cannot be substituted for the oral tablet, or vice versa, at the same dose. The outer packaging was changed to better distinguish the difference in the two formulations. Drug Safety Update (DSU) article published.
June 2016	Etonogesteral (Nexplanon)	Device found in vasculature and lung	Updated advice via DSU for healthcare professionals on how to correctly insert the implant, including an amended diagram in the SmPC that illustrates the correct angle on the arm for insertion and how to view the needle to avoid

			deep insertion.
June 2016	Dexamethasone and Ritonovir	Drug interaction: increase the risk of systemic adrenal effects	Strengthened product information warnings detailing the drug interaction of systemic adrenal effects.
April 2016	Natalizumab (Tysabri▼)	Progressive Multifocal leukoencephalophathy (PML)	Strengthened product information warnings about PML including risk factors and risk minimisation measures. A direct healthcare professional communication (DHPC) was sent out to healthcare professionals to highlight the importance of monitoring through testing patients every 6 months to reduce risk of PML.
February 2016	Proton Pump Inhibitors (PPIs): dexlansoprazole; esomeprazole; lansoprazole; omeprazole; pantoprazole; rabeprazole	Blood Chromogranin A (CgA) increase	Chromogranin A (CgA) level may interfere with investigations for neuroendocrine tumours. To avoid interference, the product information warnings were added to reduce this risk, including adding advice about stopping treatment temporarily to measure CgA levels.
January 2016	Fluvestrant (Faslodex)	Laboratory text interference	Centrally authorised product - the signal was raised by the MHRA and discussed at Pharmacovigilance Risk Assessment Committee (PRAC). Product information was strengthened to include warnings about the interference with estradiol assay.
December 2015	Cobicistat and fluticasone	Drug interaction: increase the risk of adrenal suppression	Strengthened product information warnings about the drug interaction increasing the risk of adrenal suppression after this was raised through the EU system. DSU article published.
May 2015	Warfarin	Calciphalaxis	Strengthened product information warnings and information about calciphalaxis even with normal renal function, with advice to consult

			a doctor a painful skin rash develops. DSU article published.
February 2015	Medroxyprogesterone acetate (Sayana)	Injection site atrophy	Strengthened product information warnings of injection site atrophy
November 2014	Gaviscon Infant	Constipation	Strengthened product information warnings of constipation
October 2014	Proton Pump Inhibitors (PPIs)	Subacute cutaneous lupus erythematosus (SCLE), a non-scarring dermatosis that can develop in sun-exposed areas	Strengthened product information warnings of SCLE, including information for healthcare professionals and patients or carers about lesions especially in sun-exposed areas of the skin and accompanied by arthralgia. DSU article published.
October 2014	Interferon beta (Rebif, Avonex, Betaferon, Extavia)	Thrombotic microangiopathy (TMA) and suspicion of increased risk with new formation of Rebif	Collaborative assessment with NIBSC. Need for better risk minimisation identified. Class warnings implemented for all products. Warnings to be vigilant for early signs or symptoms issued and added to the product information including diagnostic tests descriptions, treatment options and advice on the action to take. Further requirements were made for the pharmaceutical company to do further study on the possible increased risk of TMA with new formulation Rebif.
September 2014	Pregabalin	Abuse, misuse and dependence	Strengthened product information warnings regarding abuse, misuse and dependence
September 2014	Novorapid (insulin aspart)	No ADR – packaging complaint (formation of air bubbles in solution)	Centrally authorised product – referred to EMA
September 2014	Denosumab	Osteonecrosis of the jaw; monitoring for hypocalcaemia	Reminder on precautions and updated recommendations for the need of a dental examination and appropriate

			preventive dentistry before treatment
June and September 2014	Ferumoxytol	Serious hypersensitivity reactions	New recommendations to minimize risk including contraindication for patients with drug allergies and changes in the method of administration
July 2014	Fentanyl patches	Life threatening harm from accidental exposure	Reminder of potential for life-threatening harm from accidental exposure from swallowing or transfer to other individuals, particularly in children
June 2014	Chlorhexidine	Risk of chemical burns	Highlighted risk to premature infants and initiated EU review.
May 2014	Voriconazole	liver toxicity, phototoxicity, and squamous cell carcinoma	Reminder on risk of liver toxicity, phototoxicity, and squamous cell carcinoma and the importance of liver function testing and avoiding exposure to sunlight
April 2014	TNF-alpha inhibitors	Risk of tuberculosis	Precautions to be vigilant for infectious diseases: conduct pretreatment screening and close monitoring during treatment
March 2014	St John's wort and hormonal contraceptives medicines and implants	Interaction resulting in reduced contraceptive effect	Reminder about herbal products that contain St John's wort and the interaction with hormonal contraceptives
January 2014	Capecitabine	Risk of severe skin reactions	Discontinue treatment if severe skin reactions occur. Reminder to inform patients of possible severe skin reactions. Reminder advice on Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) reactions
January 2014	Temozolomide[o]	Hepatic injury and failure	Updated warnings and monitoring guidance
December 2013	Recombinant interferon-beta	Thrombotic microangiopathy	Healthcare professionals are advised to be vigilant for symptoms and signs of

			complications
November 2013	Risperidone and paliperidone	Intraoperative floppy iris syndrome (IFIS) detected during cataract surgery	Product information for risperidone and paliperidone updated to include warnings about IFIS
September 2013	Filgrastim and pegfilgrastim	Life-threatening capillary leak syndrome (CLS)	Precaution to monitor patients and healthy donors for signs and symptoms of CLS, and give standard symptomatic treatment immediately if symptoms occur

Information on the nature of risk (harms) and benefit to healthcare professionals and patients helps allow informed choices to be made about treatment options and in the management of ADRs should they occur.

Patients and health professionals reporting suspected adverse drug reactions to the Yellow Card Scheme help contribute to these important processes. Suspected reactions can be reported online at www.mhra.gov.uk/yellowcard or via the free Yellow Card app.

Yasmin and hair loss (alopecia)

After three months of being prescribed Yasmin for oral contraception, a female in her twenties suffered substantial hair loss (alopecia). She suspected this might be due to the medicine she was taking so she checked the Patient Information Leaflet (PIL) inside the packaging of her medicine, as advised to by her pharmacist when she collected her medicine - there was no mention of hair loss under the possible side effects section. She decided to go into her local community pharmacy.

Her pharmacist advised her make an appointment with her GP but at the same time also had an important discussion with her about side effects and medicines. The pharmacist asked her if she was taking any other medicines at the time – this enabled the possibility of a potential interaction between Yasmin and any other medicines to be ruled out. The pharmacist also asked her if she any of her family members had hair loss, which they did; however, she also mentioned that she had never had any history of hair loss herself.

Even though the pharmacist was not certain that Yasmin was responsible for causing hair loss, they encouraged her to complete a Yellow Card - as only a suspicion that a side effect is occurring because of a medicine is needed to complete a Yellow Card. So she went online and completed a report.

Through routine assessment by MHRA experts, her Yellow Card report triggered a more thorough review of this issue. This identified a further 14 similar reports for patients ranging from 18 to 37 years old – 7 of which were received directly from patients. At the time of the

review, most cases of hair loss were recovered or recovering. The review resulted in the Patient Information Leaflet (PIL) being updated to include hair loss (alopecia) under 'uncommon side effects': out of every 1,000 women who use Yasmin between 1 and 10 may be affected.

- Patient reporting via the Yellow Card Scheme adds value to medicines safety.
- Pharmacists and GPs have a key role to play in promoting patient safety about side effects.
- Check the PIL supplied with your medicine which lists all recognised side effects and interactions.
- Anyone is able to report suspected side effects: www.mhra.gov.uk/yellowcard
- If you are concerned about a side effect, ask your doctor or pharmacist for advice

Amlodipine and grapefruit interaction

A male patient in his sixties who drank grapefruit juice three times a day whilst taking a particular brand of amlodipine, prescribed for high blood pressure (hypertension), reported severe swelling to his legs and feet. The swelling resolved when he stopped drinking grapefruit juice.

Routine assessment of this patient's Yellow Card by MHRA experts, lead to a review of the product information for that brand of amlodipine. The MHRA received three other reports of a suspected interaction with grapefruit, all of which provided convincing /strong evidence for an interaction. The review resulted in a strengthening of interaction warnings in the Patient Information Leaflet (PIL).

It is already known that grapefruit contains a group of chemicals, furanocoumarins, which can affect drug metabolism – the amount of time it takes for a medicine to be broken down by the body. These chemicals inhibit an enzyme that breaks down some medicines, and so this can cause a higher level of the "active" medicine to be present in the body than was intended with the given dose. This can then trigger unpleasant, and sometimes serious, side effects.

Amlodipine belongs to a class of medicines known as calcium channel blockers that lower blood pressure by relaxing the muscles that make up the walls of your arteries.

Other common medicines that are known to interact with grapefruit or grapefruit juice include:

- statins such as simvastatin and atorvastatin
- some calcium channel blockers such as felodipine, isradipine, lacidipine, lercanidipine, nicardipine, nifedipine, nimodipine and verapamil. Grapefruit does not affect diltiazem.
- immunosuppressants such as clislosporin, sirolimus, tacrolimus
- entocort which contains budesonide for Crohn's diseas
- some medicines used in the treatment of cancers such as crizotinib, lapatinib, linotinib, pazopanib, sunitinib and everolimus
- aliskiren which is used to treat high blood pressure

If you eat grapefruit or drink grapefruit juice and are concerned that it may be interacting with

another of your medicines, check the Patient Information Leaflet supplied with the medicine - this lists the known interactions and side effects of a medicine and advises you what to do. If you are still unsure, check with your doctor or pharmacist before drinking grapefruit juice.

- Remember some medicines can interact with other medicine(s), food and drink
- Check the PIL supplied with your medicine which lists all recognised side effects and interactions; it also advises you what to do.
- Anyone is able to report suspected side effects: www.mhra.gov.uk/yellowcard
- If you are concerned about a side effect, ask your doctor or pharmacist for advice

Warfarin and Cranberry juice interaction

Through routine assessment of Yellow Card reports by MHRA experts in 2003, five Yellow Cards suggested an interaction of cranberry juice with warfarin. One report was of a man on warfarin who died six weeks after drinking cranberry juice daily.

Warfarin is an anticoagulant given to patients to prevent the formation of blood clots that can lead to serious and sometimes life threatening conditions such as a stroke or a heart attack. The interaction with cranberry juice led to an increase in the time taken for his blood to clot, as measured by International Normalised Ratio (INR) levels. Since the INR levels of patients on warfarin can vary it is critical that INR measurements are closely monitored.

Cranberry juice contains various antioxidants including flavinoids, which are known to inhibit the activity of an enzyme used to metabolise warfarin - cytochrome CYP2C9.

Following publicity from a published report, further Yellow Card reports were received and the MHRA conducted a review of the 12 reports of suspected interaction between warfarin and cranberry juice. Eight involved increases in INR and/or bleeding episodes, in three cases the INR was unstable and in one case the INR decreased. On review of these cases it was concluded that there was sufficient evidence of an interaction between warfarin and cranberry juice for formal advice to be issued. It was not possible to define a safe quantity or brand of cranberry juice, therefore patients taking warfarin are advised to avoid this drink unless the health benefits from the juice are considered to outweigh the risks from any change in INR and bleeding time.

MHRA advised that increased medical supervision and INR monitoring should be considered for any patient taking warfarin and having a regular intake of cranberry juice.

Similar caution should be observed with other cranberry products, such as capsules or concentrates, which might also interact with warfarin. Product information for warfarin products was updated to reflect this new advice and a warning was issued to health professionals that patients taking warfarin should limit or avoid drinking cranberry juice.

- Remember medicines can interact with other medicine(s), food and drink.
- Check the PIL supplied with your medicine which lists all recognised side effects and interactions; it also advises you what to do.

- Report suspected side effects: www.mhra.gov.uk/yellowcard
- If you are concerned about a side effect, ask your doctor or pharmacist for advice

Phenytoin and Purple Glove Syndrome (for pharmacists)

A female patient in her sixties was taking phenytoin injections for treatment of a serious epileptic condition. She developed redness and swelling in her right arm after 15-20 injections were administered at different sites and so went to speak to her local pharmacist. This was later diagnosed as purple glove syndrome - a rare condition where there is discolouration, build-up of fluid in tissue which can result in swelling, and blister formation on the hand. The swelling can lead to localised tissue death due to impaired blood supply and this can sometimes lead to disability. The pharmacist referred the patient for urgent medical treatment but also reported this to the pharmaceutical company that manufactured the medicine. The company sent the report to the MHRA because they are legally obliged to do so.

Through routine assessment by MHRA experts, this report was assessed alongside 3 other UK reports that were derived from cases reported in the medical literature and 17 other ADR reports from other countries. Following review of this issue the MHRA requested the pharmaceutical company to conduct a worldwide review of their own safety data. This analysis resulted in the addition of purple glove syndrome and warnings under possible side effects of the phenytoin product information. Although the frequency of getting purple glove syndrome is unknown; in most cases, the condition is temporary and treatment is symptomatic and supportive; reduce oedema and improved limb perfusion while monitoring for progressing vascular compromise and compartment syndrome.

- Pharmacists and GPs are in a unique position to identify and report suspected adverse drug reactions – they have a key role to play in promoting patient safety about side effects with the public.
- All serious reactions should be reported to the MHRA, but if you are not sure whether to report, send a Yellow Card anyway.
- Remember - it's quicker to report directly to the MHRA via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

Ranitidine and breast disorders (doctors)

A hospital doctor completed a Yellow Card report about a female infant suffering from recurrent episodes of bleeding from both nipples for one day every few months whilst on ranitidine for symptomatic relief of heartburn, indigestion, acid indigestion and hyperacidity. The doctor noted there was no obvious cause for this and suspected it may be related to ranitidine since it is already known to cause abnormal enlargement of male breasts (gynaecomastia).

Another Yellow Card was submitted by a GP concerning a man that experienced sore bleeding nipples which recovered upon discontinuation of ranitidine. At the time, the summary of product characteristics (SPC) – the health professional equivalent to the Patient information Leaflet (PIL) - listed 'breast symptoms in men'.

Through routine assessment by MHRA experts, these two Yellow Card reports submitted by doctors triggered a review of suspected reports of nipple disorders and gynaecomastia as the warnings at the time were considered insufficient. This ultimately resulted in new wording and strengthening of existing warnings within the updated product information to include breast symptoms and breast conditions (such as gynaecomastia and galactorrhoea – spontaneous flow of milk from breasts unassociated with childbirth or nursing). The Patient Information Leaflet was also updated to include the side effects of 'breast tenderness and or breast enlargement, breast discharge'.

- Doctors are considered the cornerstone of reporting suspected ADRs to the Yellow Card Scheme – in 2011, nearly 50% of all direct Yellow Card reports were received directly from doctors.
- GPs have an important role to play in promoting patient safety, both through reporting suspected adverse drug reactions directly as well as by informing patients how to report themselves and where to find information on suspected side effects.
- Don't delay report today: www.mhra.gov.uk/yellowcard

Varenicline (Champix▼) and somnabulism (sleep walking)

A doctor reported a case of a male patient who woke up in a police cell. The patient thought he was dreaming as he had previously experienced vivid dreams. The police officer told the man he would be breathalysed as he had fallen asleep at the wheel of his car on the side of the road. Within his report, the doctor stated that the patient had no history of psychiatric problems and no medication other than varenicline (to help him stop smoking), drugs or alcohol had been consumed by the man. The doctor suspected that this episode may have been caused by taking varenicline and so reported it to the pharmaceutical company that manufactures the medicine. The company sent the report to the MHRA because they are legally obliged to do so.

Through routine assessment by MHRA experts, this report was assessed alongside 14 other Yellow Card reports and 12 ADR reports from other countries. They contained similar suspected reactions associated with sleep walking, dreaming and nightmares. At the time, the UK product information listed abnormal dreams, insomnia and circadian rhythm sleep disorder but this was considered to be insufficient. The MHRA requested the pharmaceutical company to conduct a worldwide review of safety data. Following UK and European review, it was agreed that it was important for patients to be aware that varenicline could make them walk in their sleep with unknown frequency and a new warning of 'sleep walking' was added to the existing product information.

- Report all suspected reactions to medicines that display a black triangle (▼).The symbol is a prompt to alert health professionals to report all suspected ADRs for products displaying it regardless of the reactions severity or seriousness.
  It's useful to supply supplementary information such as relevant medical history and tests to help us with assessment.
- Remember - it's quicker to report directly to the MHRA via the Yellow Card Scheme: www.mhra.gov.uk/yellowcard

Corn plasters and skin ulceration (patients/physicians)

A podiatric physician (foot doctor) contacted the MHRA regarding concerns over medicated corn removal plasters that contained salicylic acid. Two patients who had healthy skin and had used these plasters went on to develop ulcers at the application site. This triggered a review of reactions that had been reported in association with this type of plaster in contact with healthy skin.

MHRA experts assessed the seven reports associated with salicylic acid-containing plasters, on the Yellow Card database. These Yellow Cards reported mainly suspected skin reactions. The pharmaceutical company was requested to review the safety of the product and provide a response to MHRA.

This resulted in the following new wording for the product information: “local irritation or dermatitis may occur if applied to normal healthy skin surrounding the corn. This may be controlled by temporarily discontinuing use and by careful applying only to the corn when the treatment is returned.”

- Only a suspicion is required that a medicine may be causing a reaction to report – no matter how minor: www.mhra.gov.uk/yellowcard