WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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This Newsletter is also available on our Internet website: http://www.who.int/medicines

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The WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world, including suspension and new restriction of the use of pioglitazone.

In this edition of the WHO Pharmaceuticals Newsletter, you will also find a summary of two training courses on pharmacovigilance hosted by the Pharmacy and Poisons Board, Kenya.

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Regulatory Matters

Safety of Medicines

Feature

Antipsychotic drugs

Risk of abnormal muscle movements and withdrawal symptoms in newborns

Canada. Health Canada informed health-care professionals and consumers that the prescribing information for the entire class of antipsychotic drugs is being updated. The updated labelling will contain safety information on the potential risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of their pregnancy.

Antipsychotic drugs are used to treat symptoms of psychiatric disorders such as schizophrenia and bipolar disorder. Health Canada notified the Canadian manufacturers of antipsychotic drugs (typical and atypical) to update the Product Monographs to include this safety information.

Health Canada recommended that women taking an antipsychotic and who are pregnant or thinking of becoming pregnant should talk to their doctor about their treatment and that patients should not stop taking their medication without first speaking to a health-care practitioner, as abruptly stopping an antipsychotic drug can cause serious adverse events.

The abnormal muscle movements and withdrawal symptoms in newborns include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. These symptoms can vary in seriousness. In some newborns, the symptoms may go away within hours or days and not require specific treatment, while in others the symptoms may be more severe and require medical attention.

Reference:
Advisories, Warnings and Recalls, Health Canada, 15 June 2011 (*www.hc-sc.gc.ca*).

Belatacept

Increased risk of post-transplant lymphoproliferative disorder and progressive multifocal leukoencephalopathy

USA. The US Food and Drug Administration (US FDA) announced that Bristol-Myers Squibb (BMS) informed health-care professionals about the risk evaluation and mitigation strategy (REMS) that is required for belatacept (Nulojix®) to ensure that the benefits of belatacept outweigh the risks of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML), both of which can be fatal. Patients treated with belatacept are at an increased risk for developing PTLD, predominantly involving the central nervous system. PML has been reported in patients receiving belatacept at higher than recommended doses as part of an immunosuppressant regimen.

The US FDA may require a REMS from a manufacturer before approval or post approval to ensure that the benefits of a drug or biological product outweigh its risks. Belatacept is a selective T-cell co-stimulation blocker recently approved for prophylaxis of organ rejection in adult patients receiving a kidney transplant. Belatacept is to be used in combination with basiliximab induction, mycophenolate mofetil, and corticosteroids. Belatacept is indicated for use only in transplant patients who are Epstein-Barr virus (EBV) seropositive. Use in liver transplant patients is not recommended due to an increased risk of graft loss and death. Use of belatacept for the prophylaxis of organ rejection in other transplanted organs has not been established.

The US FDA recommended verifying the patient's EBV status before initiating therapy with belatacept.

Reference:
FDA Drug Safety Communication, US FDA 7 July 2011 (*www.fda.gov*).

Dexrazoxane

Restriction in Use

Europe. The European Medicines Agency (EMA) has recommended restricting the use of dexrazoxane to adult patients with advanced or metastatic breast cancer who have already received a certain amount of the anthracyclines doxorubicin and epirubicin to treat their cancer. The Agency's Committee for Medicinal Products for Human Use (CHMP) also recommended contraindicating the use of this medicine in children.

Dexrazoxane is currently indicated for use in patients with cancer to prevent long-term toxic effects on the heart caused by treatment with doxorubicin and epirubicin.

The review of dexrazoxane was initiated following concerns that it could be linked to an increased risk of acute myeloid leukaemia (AML) and myelodysplastic syndrome (MDS). This was based on studies in the United States

reporting cases of AML and MDS in children as well as on a small number of cases of AML reported in adult breast cancer patients receiving dexrazoxane.

Following review of all available data, the Committee concluded that there was evidence of serious harm in children and adolescents receiving dexrazoxane and that the benefits of the medicine do not outweigh the risks in this age group. The Committee therefore recommended contraindicating dexrazoxane in patients under the age of 18.

With respect to the use of dexrazoxane in adults, the Committee concluded that the benefits of dexrazoxane only outweigh the risks in adult patients with advanced or metastatic breast cancer who have already received a minimum cumulative dose of 300 mg/m^2 of doxorubicin or 540 mg/m^2 of epirubicin. It also recommended that the use of dexrazoxane when used with doxorubicin should be reduced from a dose ratio of 20:1 (20 parts dexrozaxone to 1 part doxorubicin) to a ratio of 10:1. The dose ratio of dexrazoxane to epirubicin remains unchanged at 10:1. When deciding to use dexrazoxane, prescribers should carefully weigh the possible benefits in relation to the protection of the heart against the short- and long-term risks, particularly the risk of AML and MDS.

Reference:
Press release, EMA, 23 June 2011 (*www.ema.europa.eu*).

Epoetin alfa and Darbepoetin alfa

Modified dosing recommendations

USA. The US FDA notified health-care professionals of new, modified recommendations for more conservative dosing of erythropoiesis-stimulating agents (ESAs) which include epoetin alfa and darbepoetin alfa in patients with chronic kidney disease (CKD) to improve the safe use of these drugs.

ESAs treat certain types of anaemia by stimulating the bone marrow to produce red blood cells and by decreasing the need for blood transfusions. The manufacturer has revised the Boxed Warning, Warnings and Precautions, and Dosage and Administration sections of the labels for the ESAs to include this new information.

The US FDA has made these recommendations because of data showing increased risks of cardiovascular events with ESAs in this patient population. The new dosing recommendations are based on clinical trials showing that using ESAs to target a haemoglobin level of greater than 11 g/dl in patients with CKD provides no additional benefit than lower target levels, and increases the risk of experiencing serious adverse cardiovascular events, such as heart attack or stroke.

The US FDA recommended that health-care professionals should weigh the possible benefits of using ESAs to decrease the need for red blood cell transfusions in CKD patients against the increased risks for serious cardiovascular events, and should inform their patients of the current understanding of potential risks and benefits. Therapy should be individualized to the patient and the lowest possible ESA dose given to reduce the need for transfusions.

(See WHO Pharmaceuticals Newsletter No. 5 and 6, 2008 for the review of the safety of epoetin alfa in the USA and reports in WHO Global ICSR database.)

Reference:
FDA Drug Safety Communication, US FDA 24 June 2011 (*www.fda.gov*).

Finasteride and Dutasteride

Increased risk of prostate cancer

USA. The US FDA notified health-care professionals that the Warnings and Precautions section of the labels for the 5-alpha reductase inhibitor (5-ARI) class of drugs which include finasteride and dutasteride has been revised to include new safety information about the increased risk of being diagnosed with a more serious form of prostate cancer (high-grade prostate cancer).

These drugs are marketed under the brand-names Proscar®, Propecia®, Avodart®, and Jalyn® in the USA. Proscar, Avodart, and Jalyn are approved to improve symptoms of an enlarged prostate gland (benign prostatic hyperplasia or BPH). Proscar and Avodart are also approved to reduce the risk of urinary retention or surgery related to an enlarged prostate. Propecia is approved to treat male pattern hair loss.

The new safety information is based on the US FDA's review of two large, randomized controlled trials–the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial.

The US FDA recommended that prior to initiating therapy with 5-ARIs, there should be appropriate evaluation to rule out other urological conditions,

including prostate cancer, that might mimic benign prostatic hyperplasia (BPH).

(See WHO Pharmaceuticals Newsletter No. 6, 2009 for finasteride's potential risk of male breast cancer in the UK.)

Reference:
FDA Drug Safety Communication, US FDA 9 June 2011 (*www.fda.gov*).

H1N1 influenza vaccine (Pandemrix)

Restricting use of Pandemrix

Europe. The EMA announced that the CHMP finalized its review of Pandemrix and narcolepsy and recommended that in persons under 20 years of age Pandemrix may only be used if the recommended seasonal trivalent influenza vaccine is not available and if immunization against H1N1 is still needed (e.g. in persons at risk of the complications of infection). The CHMP confirmed that overall the benefit-risk balance of Pandemrix remains positive.

The CHMP considered all available data on the possible association between Pandemrix and narcolepsy and the impact on the overall benefit-risk balance of Pandemrix. These included the results of epidemiological studies carried out in Finland and Sweden, analysis of safety surveillance data performed in several Member States and case reports from across the European Union (EU). They also included the preliminary results of an epidemiological study of narcolepsy and pandemic vaccines in eight EU Member States, coordinated by the European Centre for Disease Prevention and Control (ECDC) through a network of research and public health institutions (VAESCO).

The CHMP also took advice from a specially convened meeting of experts in fields such as paediatric neurology, vaccinology, immunology, sleep disorders, infectious diseases, epidemiology, as well as experts from Health Canada, WHO and the ECDC, to consider the latest available data regarding the possible link between Pandemrix and narcolepsy.

The CHMP noted that similar epidemiological studies have not been completed in other countries. The preliminary results of the VAESCO study confirmed the signal in Finland. Results are still preliminary and do not allow conclusions in other countries (where vaccination coverage with Pandemrix was lower), but the final results of the VAESCO study are still awaited. The CHMP stressed that further research is necessary.

The marketing authorization holder for Pandemrix, GlaxoSmithKline, is carrying out a retrospective cohort study in Canada, where an equivalent H1N1 vaccine (Arepanrix) was widely used. The company is required to carry out non-clinical and clinical studies in order to further explore the association between Pandemrix vaccination and narcolepsy.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for the study on the suspected link between narcolepsy and Pandemrix in Europe.)

Reference:
Press release, EMA, 21 July 2011 (*www.ema.europa.eu*).

Leflunomide

Wash-out procedure added to the data sheet

New Zealand. New Zealand Medicines and Medical Devices Safety Authority (Medsafe) advised that prescribers are reminded that if serious adverse reactions occur, leflunomide must be stopped and a cholestyramine or charcoal wash-out procedure initiated immediately. In addition, rheumatology advice should be sought for all patients experiencing serious adverse reactions to leflunomide. Medsafe also encouraged prescribers to familiarize themselves with the prescribing information for leflunomide.

Leflunomide is a disease modifying anti-rheumatic drug indicated for the treatment of rheumatoid arthritis and active psoriatic arthritis. Leflunomide can cause serious and potentially life-threatening adverse reactions involving the liver, blood, lungs and skin. Due to its immunosuppressant effects leflunomide can also cause life-threatening infections, particularly when given in combination with other immunosuppressant medicines. As leflunomide has a very long half-life (usually 1-4 weeks), adverse reactions can occur or persist long after leflunomide is discontinued.

According to Medsafe, safety information has recently been added to the data sheet to include the following:

• Side-effects may occur more commonly if leflunomide is given concomitantly with other hepatotoxic or haematotoxic medicines. Monitoring guidelines contained in the leflunomide data sheet should be carefully followed.

• Interstitial pneumonitis may occur more frequently with concomitant use of methotrexate.

• A wash-out procedure should be used for all serious adverse reactions. This information is

included in a new subsection of the data sheet "Washout procedure for severe adverse reactions".

(See WHO Pharmaceuticals Newsletter No. 4, 2010 for new boxed warning for severe liver injury in the USA and reports in WHO Global ICSR database.)

Reference:
Prescriber Update Vol. 32 No. 2, June 2011 (*www.medsafe.govt.nz*).

Linezolid

Serious CNS reactions possible in patients taking certain psychiatric medications

USA. The US FDA announced that the Agency has received reports of serious central nervous system (CNS) reactions when the antibacterial drug linezolid (Zyvox®) is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Safety information about this potential drug interaction and important drug usage recommendations for emergency and non-emergency situations are being added to the drug labels for serotonergic psychiatric medications and linezolid.

Linezolid is used to treat infections, including pneumonia, infections of the skin, and infections caused by a resistant bacterium (Enterococcus faecium). It is a reversible monoamine oxidase inhibitor (MAOI). Although the exact mechanism of this drug interaction is unknown, linezolid inhibits the action of monoamine oxidase A. It is believed that when linezolid is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity. This is referred to as Serotonin Syndrome — signs and symptoms include mental changes (confusion, hyperactivity, memory problems), muscle twitching, excessive sweating, shivering or shaking, diarrhea, trouble with coordination and/or fever.

The US FDA recommended that linezolid should generally not be given to patients taking serotonergic drugs; however patients should not stop taking their serotonergic psychiatric medicine without first talking to a health-care professional.

Reference:
FDA Drug Safety Communication, US FDA 26 July 2011 (*www.fda.gov*).

Methylene blue

Serious CNS reactions possible in patients Taking certain psychiatric medications

USA. The US FDA announced that the Agency has received reports of CNS reactions when the drug methylene blue is given to patients taking psychiatric medications that work through the serotonin system of the brain (serotonergic psychiatric medications). Safety information about this potential drug interaction and important drug usage recommendations for emergency and non-emergency situations are being added to the drug labels for serotonergic psychiatric medications.

Methylene blue is used to treat methemoglobinemia, vasoplegic syndrome, ifosfamide-induced encephalopathy, and cyanide poisoning. It is also used as a dye in therapeutic and diagnostic applications. Methylene blue is a potent, reversible MAOI. It is believed that when methylene blue is given to patients taking serotonergic psychiatric medications, high levels of serotonin can build up in the brain, causing toxicity (Serotonin Syndrome).

The US FDA recommended that methylene blue should generally not be given to patients taking serotonergic drugs. However, there are some conditions that may be life-threatening or require urgent treatment with methylene blue such as when it is used in the emergency treatment of methemoglobinemia, ifosfamide-induced encephalopathy, or cyanide poisoning. The US FDA also recommended that patients should not stop taking their serotonergic psychiatric medicine without first talking to a health-care professional.

Reference:
FDA Drug Safety Communication, US FDA 26 July 2011 (*www.fda.gov*).

Metoclopramide

Stronger warnings on risk of abnormal muscle movements

Canada. Health Canada informed health professionals and consumers that the labelling information for the drug metoclopramide is updated to include stronger warnings on the risk of a movement disorder known as "tardive dyskinesia." The risk increases with longer treatment and is higher in the elderly, especially elderly women.

Tardive dyskinesia usually appears as involuntary movements of the tongue, face, mouth or jaw. These movements can include lip smacking, chewing, or puckering, or sticking out of the tongue. Sometimes, movements can include the torso or limbs, such as leg shaking. There are no known treatments for tardive dyskinesia once it has become established.

Tardive dyskinesia is a known side-effect associated with metoclopramide. The current prescribing information contains information on this risk. Health Canada is working with the Canadian manufacturers to include stronger, more detailed warnings in the drug labelling that contain the following information:

• Tardive dyskinesia may develop in patients treated with metoclopramide. The elderly, especially elderly women, appear to be at increased risk.

• The risk appears to increase with treatment length and the total amount of drug taken.

• Tardive dyskinesia is more likely to be irreversible with long-term treatment (over 12 weeks).

• Less frequently, tardive dyskinesia can develop with short term treatment at low doses; in these cases, the symptoms are more likely to disappear either partially or completely over time, once treatment has been stopped.

• Tardive dyskinesia may not be easy to recognize in its early stages.

• Metoclopramide treatment beyond 12 weeks should be avoided, unless the benefit is judged to outweigh the risk.

Metoclopramide is most commonly used to treat digestive problems associated with a stomach that empties too slowly. Health Canada reminded health-care professionals that metoclopramide is not authorized in Canada for the following: treatment of hiccups, diabetic gastroparesis (partial paralysis of the stomach), nausea and vomiting in pregnancy, or for symptoms of bloating or constipation associated with eating disorders.

(See WHO Pharmaceuticals Newsletter No. 2, 2009 for warning against chronic use in the USA and reports in WHO Global ICSR database.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 20 July 2011 (www.hc-sc.gc.ca).

Nimesulide

Use to be restricted to treatment of acute pain and primary dysmenorrhoea

Europe. The CHMP has concluded that the benefits of systemic nimesulide-containing medicines continue to outweigh their risks in the treatment of patients with acute pain and primary dysmenorrhoea. However, these medicines should no longer be used for the symptomatic treatment of osteoarthritis.

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID) that has been used to treat acute pain, painful osteoarthritis and primary dysmenorrhoea.

The CHMP reviewed results of epidemiological studies conducted by the marketing authorization holder at the request of the Committee in 2007, all available reports on adverse drug reactions and data from the published literature. The Committee noted that, in treatment of acute pain, nimesulide is as effective as other NSAID pain killers, such as diclofenac, ibuprofen and naproxen. In terms of safety, the CHMP noted that nimesulide has the same risk of gastrointestinal toxicity as other NSAIDs.

The CHMP concluded that nimesulide was associated with an increased risk of liver toxicity compared with other anti-inflammatory treatments. The Committee had previously imposed several restrictions on the use of systemic nimesulide in order to reduce risks of liver injury. Having reviewed all available data, the CHMP is now recommending, as a further restriction, that systemic nimesulide should no longer be used for the treatment of painful osteoarthritis. The Committee considered that the use of systemic nimesulide for the treatment of this chronic condition, would increase the risk of the medicines being used for long-term treatment, with a consequent increase in the risk of liver injury.

(See WHO Pharmaceuticals Newsletter No. 3, 5 and 6, 2007 for review and regulatory outcome in Ireland and EU.)

Reference:
Press release, EMA, 23 June 2011 (*www.ema.europa.eu*).

Paracetamol

Toxicity in children

New Zealand (1). Medsafe reported that reports over the last 12 months describing serious adverse reactions in children due to paracetamol toxicity highlight the importance of using this medicine appropriately.

Paracetamol liquid remains one of the most commonly used medicines for minor illnesses in children. However, toxicity can easily occur if there is confusion over the strength of paracetamol liquid used or the need to calculate or measure the dose.

New Zealand National Poisons Centre data suggest that the number of unintentional chronic overdoses involving paracetamol has increased in children over the last five years. A further breakdown by age indicates this increase is greatest in children aged 0–2 years.

According to Medsafe, the risk of unintentional overdosing in children can be reduced by:

• Prescribing small volumes of paracetamol liquid to be dispensed.

• Prescribing paracetamol for each child rather than providing a large volume of liquid for several children or an entire family.

• Reducing the need for parents to calculate doses and convert to the number of mL to administer. A specific dose should always be stated on the prescription.

Medsafe advised health-care professionals to inform parents that paracetamol should only be given to children for the treatment of pain and pyrexia, and to ensure the correct dose is given at the correct frequency. Prescribers are also advised to consider limiting the volume of paracetamol liquid prescribed to children to a maximum of 200mL per dispensing. This approach may help reduce the number of poisonings needing hospitalization and will reduce the risk of parents using expired medicine.

UK (2). The MHRA announced that updated dosing for paediatric paracetamol liquids has been developed to ensure children receive the optimum dose for their age.

According to the MHRA, the current recommended doses consist of wide age bands with the option to receive 5 mL or 10 mL within each dose range. As a result, children who are light for their age and receive the maximum recommended dose will receive an amount per kg bodyweight that differs from older, heavier children taking the lower recommended dose within that age band. Consequently, lighter children may currently be receiving a higher dose than needed for an effective therapeutic result, if the parent or carer decides to use the larger dosing option. To address this, the MHRA revised the dosing for liquid paracetamol products for children to one that is based on narrower age bands with a single dosing option per band.

(See WHO Pharmaceuticals Newsletter No. 1, 2011 for limitation of dosing and the potential risk of severe liver failure in the USA.)

References:

(1) Prescriber Update Vol. 32 No. 2, June 2011 (www.medsafe.govt.nz).
(2) Drug Safety Update, July 2011, Volume 4, issue 12, A2, MHRA (*www.mhra.gov.uk*).

Pioglitazone

Suspension of pioglitazone in France; CHMP requests risk-characterization study in Europe

France (1). The French Health Products Safety Agency (Afssaps) decided to suspend the use in France of medicines containing pioglitazone (Actos® and Competact®). Pioglitazone is indicated in glycaemic control in diabetic patients. It was authorized as part of a centralized European procedure.

According to Afssaps, available pharmacovigilance data and the new study results of the Caisse Nationale d'Assurance Maladie (CNAMTS) confirmed low risk of occurrence of bladder cancer during the use of pioglitazone. Finding that the risk / benefit ratio of this product was now negative, Afssaps, on the advice of the commission for market authorization (AMM) and the National Commission of Pharmacovigilance, decided to suspend the use of pioglitazone.

The decision is effective 11 July 2011 to allow patients to contact their doctor who will adjust their diabetes treatment.

Europe (2). The EMA announced that the CHMP confirmed that anti-diabetic pioglitazone-containing medicines remain a valid treatment option for certain patients with type 2 diabetes but that there is a small increased risk of bladder cancer in patients taking these medicines. However, the CHMP also concluded that the small increased risk could be reduced by appropriate patient selection and exclusion, including a requirement for

periodic review of the efficacy and safety of the individual patient's treatment.

The EMA advised prescribers not to use these medicines in patients with current or a history of bladder cancer or in patients with uninvestigated macroscopic haematuria. Risk factors for bladder cancer should be assessed before initiating pioglitazone treatment. In light of age-related risks, the balance of benefits and risks should be considered carefully both before initiating and during treatment in the elderly. Prescribers should review the treatment of patients on pioglitazone after three to six months (and regularly afterwards) to ensure that only patients who are deriving sufficient benefit continue to take it.

The CHMP reviewed all available data on the occurrence of bladder cancer, including results of preclinical studies, clinical studies, epidemiological studies and spontaneous reports. The Committee also considered the advice from its Scientific Advisory Group (SAG) on Diabetes/Endocrinology.

In line with the recommendations of the SAG, the CHMP concluded that there are some patients who cannot be adequately treated by other treatments and who will benefit from treatment with pioglitazone. The CHMP agreed that it was not possible to further restrict the current indications of pioglitazone. Instead, prescribers are advised to carefully select patients and monitor response to treatment. In patients responding to treatment, the CHMP concluded that the benefits outweigh the risks.

The CHMP has asked the marketing authorization holder to conduct a pan-European epidemiological study focussing on more robust characterization of the risk, in particular the risk period and risk with increasing age, to inform the evidence-base for risk minimization measures.

The US FDA and Health Canada announced that they are undertaking a review of pioglitazone and potential risk of bladder cancer.

(See WHO Pharmaceuticals Newsletter No. 5, 2010 for ongoing safety review on potential increased risk of bladder cancer in the USA and No. 1, 2011 for risk of cardiac failure in the UK.)

Reports in WHO Global ICSR database, Vigibase:

Pioglitazone

Number of reports: 63 (PT Bladder carcinoma)

References:

(1) Suspension de l'utilisation en France des médicaments contenant de la pioglitazone, Afssaps, 9 June 2011 (www.afssaps.fr).
(2) Press release, EMA, 21 July 2011 (www.ema.europa.eu).
(3) FDA Drug Safety Communication, US FDA 15 June 2011 (www.fda.gov).
(4) Advisories, Warnings and Recalls, Health Canada, 17 June 2011 (www.hc-sc.gc.ca).

Simvastatin

New restrictions, contraindications, and dose limitations

USA. The US FDA notified health-care professionals that it is recommending limiting the use of the highest approved dose of the cholesterol-lowering medication simvastatin 80 mg because of increased risk of muscle damage. Patients taking simvastatin 80 mg daily have an increased risk of myopathy compared to patients taking lower doses of this drug or other drugs in the same class. This risk appears to be higher during the first year of treatment, is often the result of interactions with certain medicines, and is frequently associated with a genetic predisposition towards simvastatin-related myopathy. The most serious form of myopathy, called rhabdomyolysis, can damage the kidneys and lead to kidney failure which can be fatal.

The US FDA is requiring changes to the simvastatin label to add new contraindications (should not be used with certain medications) and dose limitations for using simvastatin with certain medicines. Simvastatin 80 mg should be used only in patients who have been taking this dose for 12 months or more without evidence of muscle injury (myopathy).

The US FDA recommended that Simvastatin 80 mg should not be started in new patients, including patients already taking lower doses of the drug.

Reference:

FDA Drug Safety Communication, US FDA 8 June 2011 (www.fda.gov).

Simvastatin and Atorvastatin

Interactions: reports of serious myopathy

New Zealand. Medsafe reminded prescribers of the potential for serious adverse reactions when statins are prescribed with medicines that inhibit the CYP3A4 isoenzyme.

According to Medsafe, recent reports to the Centre for Adverse Reactions Monitoring

(CARM) indicate that the concomitant treatment with medicines that interact with simvastatin or atorvastatin has led to serious myopathies. These reports have included life-threatening and fatal cases of rhabdomyolysis. In some cases more than one interacting medicine was prescribed.

The adverse reaction reports describe common situations such as:

• The use of macrolides for acute infection without stopping the patient's regular simvastatin.

• Initiating diltiazem in patients taking over 40 mg simvastatin daily.

• A lack of clarity in the treatment plan when care of the patient is transferred from primary to secondary care.

The metabolism of simvastatin and atorvastatin is affected by inhibitors of CYP3A4, such as macrolide antibiotics, azole antifungals, ciclosporin, amiodarone, protease inhibitors and grapefruit juice. Although diltiazem is considered to be a weak inhibitor of CYP3A4, the risk of adverse reactions increases with higher doses of statin.

(See WHO Pharmaceuticals Newsletter No. 2, 2010 for increased risk of muscle injury with high doses in the USA and No. 3, 2010 for increased risk of myopathy at high dose in the UK.)

Reference:
Prescriber Update Vol. 32 No. 2, June 2011 (*www.medsafe.govt.nz*).

Tamoxifen

CYP2D6 interactions and variable clinical response

New Zealand. Medsafe announced that recent evidence suggests there is a potential risk for higher rates of disease recurrence and death related to breast cancer in women taking tamoxifen concomitantly with CYP2D6 inhibitors. It is noted in the literature that CYP2D6 inhibitors such as selective serotonin reuptake inhibitors (SSRIs) are commonly used concomitantly with tamoxifen.

The interaction centers on endoxifen, an important active metabolite that contributes significantly to the efficacy of tamoxifen and which is produced by the metabolism of tamoxifen via CYP2D6. Drugs that inhibit CYP2D6 can therefore lead to reduced plasma concentrations of endoxifen and reduced action.

A study involving over 1,200 women found that the 2-year breast cancer recurrence rate was 1.9 times higher in patients receiving both tamoxifen and a CYP2D6 inhibitor, compared to those receiving tamoxifen only (13.9% vs 7.5%). In addition the breast cancer recurrence rate was 2.2 times higher in women receiving a moderate to potent CYP2D6 inhibitor. A more recent population-based cohort study (n=2430) found an increased risk of death related to breast cancer in women taking tamoxifen and concomitant paroxetine. A dose response relationship was apparent, with relative increases in death related to breast cancer associated with increased time of overlapping tamoxifen and paroxetine treatment.

Medsafe advised prescribers to avoid concomitant use of potent CYP2D6 inhibitors in women taking tamoxifen for breast cancer (eg paroxetine). Medsafe also advised that if antidepressant treatment is required, preference should be given to those that show little or no inhibition of CYP2D6.

(See WHO Pharmaceuticals Newsletter No. 6, 2010 for drug interactions with CYP2D6 inhibitors in the UK.)

Reference:
Prescriber Update Vol. 32 No. 2, June 2011 (*www.medsafe.govt.nz*).

Thalidomide

Risk of arterial and venous thromboembolism

UK. The MHRA reported that patients treated with thalidomide have an increased risk of arterial thromboembolism, including myocardial infarction and cerebrovascular events, in addition to the established risk of venous thromboembolism. The MHRA advised that health-care professionals should consider venous and arterial thrombotic risk and administer antithrombotic prophylaxis for at least the first five months in patients commencing thalidomide

Thalidomide is licensed throughout the EU for use in combination with melphalan and prednisone as first-line treatment for patients with untreated multiple myeloma who are 65 years or older, or those who are ineligible for high-dose chemotherapy. Thalidomide is an immunomodulatory agent, which has antineoplastic, antiangiogenic, and antierythropoietic properties.

According to the MHRA, a recent review of global postmarketing data has shown that approximately one third of all thromboembolic reactions reported in association with thalidomide were arterial, most

of which were myocardial infarction and cerebrovascular events (54.2% and 19.8%, respectively). Evidence from postmarketing case reports suggests that the risk of arterial thrombotic and thromboembolic reactions is greatest during the first five months of therapy. Antithrombotic prophylaxis should therefore be administered for at least the first five months of treatment, especially in patients with thrombotic risk factors in addition to multiple myeloma. The MHRA also reported that a history of thromboembolic events, or concomitant use of erythropoietic agents or other agents such as hormone-replacement therapy, may increase the risk of thromboembolic events. These agents should be used with caution in patients with multiple myeloma who are receiving thalidomide.

Reference:
Drug Safety Update Vol. 4, No. 12 , A1, MHRA, July 2011 (www.mhra.gov.uk).

Valproate sodium, divalproex sodium, valproic acid

Risk of impaired cognitive development in children exposed *in utero*

USA. The US FDA notified health-care professionals that children born to mothers who take the anti-seizure medication valproate sodium or related products (valproic acid and divalproex sodium) during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications during pregnancy. This conclusion is based on the results of epidemiologic studies that show that children born to mothers who took valproate sodium or related products throughout their pregnancy tend to score lower on cognitive tests (IQ and other tests) than children born to mothers who took other anti-seizure medications during pregnancy.

In 2009, the US FDA warned against use of valproate during pregnancy because of the risk for neural tube defects. Valproate products are approved to treat seizures, and manic or mixed episodes associated with bipolar disorder (manic-depressive disorder), and to prevent migraine headaches. They are also used off-label (for unapproved uses) for other conditions, particularly for other psychiatric conditions.

The US FDA recommended that health-care professionals should inform women of childbearing age of the increased risk for adverse effects on cognitive development with prenatal valproate exposure, and should continue to counsel women of childbearing potential taking valproate about the increased risk of major malformations, including neural tube defects, when valproate is used during pregnancy. In addition, health-care professionals should weigh the benefits and risks of valproate when prescribing this drug to women of childbearing age, particularly when treating a condition not usually associated with permanent injury or death. Alternative medications that have a lower risk of adverse birth outcomes should be considered.

(See WHO Pharmaceuticals Newsletter No. 1, 2010 for increased risk of neural tube defects and other major malformations in the USA.)

Reference:
FDA Drug Safety Communication, US FDA 30 June 2011 (www.fda.gov).

Varenicline

Risk of certain cardiovascular adverse events

USA. The US FDA notified the public that the smoking cessation aid varenicline (Chantix®) may be associated with a small, increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The Agency has approved an updated drug label for varenicline to include information about the efficacy and safety of the drug in two patient populations who may benefit greatly from giving up smoking—those with cardiovascular disease and those with chronic obstructive pulmonary disease (COPD). The updated label now also includes alternative directions for patients to select a 'quit smoking' date.

The US FDA reviewed a randomized clinical trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. In this trial, varenicline was effective in helping patients quit smoking and remain abstinent from smoking for as long as one year. Cardiovascular adverse events were infrequent overall; however, certain events, including heart attack, were reported more frequently in patients treated with varenicline than in patients treated with placebo.

The US FDA advised that health-care professionals should be aware that smoking is an independent and major risk factor for cardiovascular disease, and smoking cessation is of particular importance in this patient population. The known benefits of varenicline should be weighed against its potential risks when deciding to use the drug in smokers with cardiovascular disease. The US

FDA also advised that patients taking varenicline should contact their health-care professional if they experience new or worsening symptoms of cardiovascular disease.

The US FDA is continuing to evaluate the cardiovascular safety of varenicline and is requiring the manufacturer to conduct a large, combined analysis (meta-analysis) of randomized, placebo-controlled trials.

Reports in WHO Global ICSR database, Vigibase:

Varenicline

Number of reports: 10351 (SOC Cardiovascular Disorders, General, SOC Central & Peripheral Nervous System Disorders, SOC Heart Rate and Rhythm Disorders)

Most reported reactions (number of events):

Headache:	*3687*
Dizziness:	*2609*
Hypertension:	*958*
Tremor:	*860*
Palpitation:	*695*
Coma:	*615*
Muscle contractions involuntary:	*564*
Paraesthesia:	*537*
Convulsions grand mal:	*529*
Tachycardia:	*495*

(See earlier issues of the WHO Pharmaceuticals Newsletter for worldwide reports of neuropsychiatric events with varenicline: Nos. 1, 3, 4, 5 and 6, 2008; Nos. 1 and 4, 2009; No.4, 2010.)

Reference:

FDA Drug Safety Communication, US FDA 22 July 2011 (www.fda.gov).

Amiodarone

The development of ocular adverse effects

New Zealand. Medsafe reported that amiodarone use is associated with the development of ocular adverse effects including optic neuropathy (which occurs rarely) and corneal deposits (which occur in most patients). Medsafe advised that all patients experiencing new or worsening visual symptoms while taking amiodarone should be referred for ophthalmological assessment and that amiodarone should be stopped if optic neuropathy is confirmed due to the potential for progression to permanent visual loss.

The CARM has received 51 reports of eye-related adverse reactions to amiodarone up to April 2011. These include three reports of optic neuropathy, 19 reports of corneal deposits and 12 reports of abnormal vision. Reports to CARM highlight the variable presentation of amiodarone associated optic neuropathy. One case involved a 63-year-old woman who developed sudden onset of left sided visual loss two weeks after stopping amiodarone (which she had received for six weeks prior to successful cardioversion). A second case involved a 67-year-old man who first noticed visual changes four months after starting amiodarone. Initial examination found reduced visual acuity in the right eye. One year later this had progressed to complete visual loss in the right eye and substantial visual loss in the left eye.

Patients treated with amiodarone may also be predisposed to anterior ischaemic optic neuropathy due to their underlying cardiovascular risk factors. The differentiation of this cause of visual loss from a drug induced optic neuropathy can be difficult but both diseases can result in severe visual loss.

Amiodarone monitoring guidelines in New Zealand recommend that baseline eye examinations be performed in patients with pre-existing visual impairment. Follow-up eye examinations are recommended for all patients who develop visual symptoms while taking amiodarone.

Medsafe advised that prescribers are reminded to enquire about visual symptoms during follow-up visits and to continue to report suspected serious and/or unexpected adverse reactions to amiodarone to CARM.

Reference:
Prescriber Update Vol. 32 No. 2, June 2011 (*www.medsafe.govt.nz*).

Clozapine

The importance of treating constipation

New Zealand. Medsafe reminded prescribers of the importance of treating constipation in patients taking clozapine to prevent potentially life-threatening complications. Constipation is a very common adverse effect related to clozapine use, occurring in 14-60% of patients. In rare cases complications can be fatal. Risk factors include recent initiation of clozapine treatment, higher clozapine doses, concomitant use of anticholinergics (e.g. benztropine and tricyclic antidepressants), and concurrent illness.

Since 2007, when Medsafe last issued advice on this topic, CARM has continued to receive reports of clozapine-induced GI hypomotility-related adverse reactions. From 1 April 2007 to 31 March 2011, CARM received 14 reports of GI hypomotility for which clozapine was assessed as causally associated; two reports were life-threatening and two reported a fatal outcome.

Medsafe advised that prior to initiation of treatment with clozapine, a gastrointestinal history and abdominal examination should be performed. Medsafe also advised that patients should be warned about the risks of constipation and given information on diet, exercise and fluid intake. Pre-existing constipation should be addressed before starting treatment with clozapine. Any patients taking clozapine should be asked about their bowel habits regularly, especially in the first few months of treatment. However, the risk continues with ongoing use; therefore all patients taking clozapine need to be asked about their bowel habits on an ongoing basis.

Medsafe also advised that appropriate laxatives should be prescribed to treat constipation and need to be reviewed regularly. The most commonly reported signs and symptoms of serious complications include: moderate to severe abdominal pain, abdominal distension, vomiting, paradoxical "overflow" diarrhoea, reduced appetite, nausea. Patients with these signs and symptoms require urgent medical referral and treatment as complications such as septic shock can occur.

(See WHO Pharmaceuticals Newsletter No.6, 2007 for warning on gastrointestinal effects of clozapine in New Zealand and No. 1, 2011 for risk of life-threatening gastrointestinal hypomotility in Canada.)

Reference:
Prescriber Update Vol. 32 No. 2, June 2011 (*www.medsafe.govt.nz*).

Dronedarone

Increased risk of death or serious cardiovascular events

Canada (1). Health Canada announced that it is reviewing the heart-related safety of dronedarone (Multaq). Health Canada is aware of that the company (Sanofi) has decided to stop the PALLAS (Permanent Atrial fibrillation outcome Study using dronedarone on top of standard therapy) Phase IIIb clinical trial. The study was stopped because of a higher number of severe cardiovascular-related adverse events in patients taking drondarone relative to patients not taking drondarone.

The PALLAS study was investigating the use of drondarone in patients over 65 years of age with permanent atrial fibrillation in addition to other forms of heart disease. Permanent atrial fibrillation in this trial is atrial fibrillation that has not responded to any form of medical therapy for at least six months. In Canada, drondarone is authorized only for the treatment of patients with a history of, or who currently have various forms of intermittent atrial fibrillation ("non-permanent atrial fibrillation").

Health Canada is currently evaluating the available information with respect to drondarone and the potential for an increased risk of cardiovascular events.

USA (2). The FDA notified health-care professionals that it is reviewing data from a clinical trial that evaluated the effects of the antiarrhythmic drug dronedarone (Multaq®) in patients with permanent atrial fibrillation. The study was stopped early after the data monitoring committee found a two-fold increase in death, as well as two-fold increases in stroke and hospitalization for heart failure in patients receiving Multaq compared to patients taking a placebo. The US FDA is evaluating whether and how the preliminary results of the PALLAS study apply to patients taking dronedarone for paroxysmal or persistent atrial fibrillation or atrial flutter. The US FDA will update the public when more information is available.

References:

(1) Advisories, Warnings and Recalls, Health Canada, 2 June 2011 (www.hc-sc.gc.ca).
(2) FDA Drug Safety Communication, US FDA 21 July 2011 (www.fda.gov).

EMA plans public access to information on ADR

Europa. The EMA has published its plans for granting public access to the information held in its databases EudraVigilance and EudraVigilance Veterinary databases. These are the central repositories for reports of suspected adverse reactions related to medicines authorized in the European Economic Area and medicines being studied in clinical trials.

For human medicines, the Agency plans to produce monthly reports summarising the information held in EudraVigilance for all medicines authorized centrally via the Agency by the end of this year, extending this to searchable reports for all medicines by the end of 2012.

The Agency plans to make further improvements to the search and data-output functions and to supply the pharmaceutical industry with access to tools allowing the detection and analysis of signals on adverse reactions to human medicines by 2015, subject to budget being available. The Agency will consider providing access to data for research purposes on a case-by-case basis, in line with its objective of protecting public health.

Reference:

Press release, EMA, 8 July 2011 (*www.ema.europa.eu*).

Drospirenone-containing combined oral contraceptives

Possible increased risk of venous thromboembolism

USA (1). The US FDA announced that the Agency is aware of two newly published studies that evaluated the risk of venous thromboembolism (VTE) in women who use birth control pills that contain drospirenone.

The two recently published studies looked at whether there is a higher risk of blood clots in women taking birth control pills containing the progestin drospirenone when compared to women taking birth control pills containing a different progestin called levonorgestrel. These two new studies reported that there is a greater risk of VTE associated with birth control pills that contain drospirenone. This risk is reported to be up to two to three times greater than the risk of VTE associated with using levonorgestrel-containing pills.

The US FDA will look at all currently available information to fully assess the risks and benefits of drospirenone-containing birth control pills. The US FDA will continue to communicate any new safety information to the public as it becomes available.

UK (2). The MHRA reported that epidemiological studies have shown that the risk of venous thromboembolism (VTE) for drospirenone-containing combined oral contraceptives (COCs), including Yasmin®, is higher than for levonorgestrel-containing COCs (so-called 'second generation' pills) and may be similar to the risk for COCs that contain desogestrel or gestodene (so-called 'third generation' pills). The risk of VTE with Yasmin® remains very small and, like other oral contraceptives, is less than that associated with pregnancy.

The MHRA advised that prescribers should be aware of the updated information when discussing the most suitable type of contraceptive for any woman who wants to start or switch contraception.

(See WHO Pharmaceuticals Newsletter No.3, 2010 for update on the risk of venous thromboembolism in UK.)

References:

(1) FDA Drug Safety Communication, US FDA 31 May 2011 (www.fda.gov).
(2) Drug Safety Update Vol. 4, No. 11, A2, MHRA, June 2011, (www.mhra.gov.uk).

Liraglutide [rDNA origin] Injection

Risk of thyroid C-cell tumors, acute pancreatitis

USA. The US FDA announced that Novo Nordisk reminded health-care professionals of important safety information about liraglutide [rDNA origin] injection (Victoza®) required in a Risk Evaluation and Mitigation Strategy (REMS). The letter is being sent because a recent assessment of health-care providers showed that some primary care providers are not fully aware of the serious risks associated with the use of Victoza®.

Liraglutide [rDNA origin] injection is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Liraglutide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors at clinically relevant exposures in both genders of rats and mice. It is unknown whether Victoza® causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC), in humans. Additionally, in clinical trials studying Victoza®, there were more cases of pancreatitis in patients treated with Victoza® than in patients treated with comparators.

The US FDA recommended that patients with thyroid nodules noted on physical examination or neck imaging obtained for other reasons should be referred to an endocrinologist for further evaluation. Although routine monitoring of serum calcitonin is of uncertain value in patients treated with Victoza®, if serum calcitonin is measured and found to be elevated, the patient should be referred to an endocrinologist for further evaluation.

After initiation of Victoza®, and after dose increases, patients should be observed carefully for signs and symptoms of pancreatitis (including persistent severe abdominal pain, sometimes radiating to the back, and which may or may not be accompanied by vomiting).

Reference:

FDA Drug Safety Communication, US FDA 13 June 2011 (www.fda.gov).

Rituximab

Fatal infusion related reactions in patients with rheumatoid arthritis

Canada. Health Canada and Hoffmann-La Roche Limited have announced important new safety information regarding fatal infusion related reactions following the use of rituximab (Rituxan®) in **rheumatoid arthritis** (RA) patients.

According to Health Canada, post-marketing cases of fatal infusion related reactions have been reported in patients with RA treated with rituximab. It is recommended as follows:

• If anaphylaxis or other serious hypersensitivity/infusion reaction occurs, administration of rituximab should be stopped immediately, and appropriate medical management should be initiated.

• Infusions should not be administered unless they are in a setting where resuscitation equipment is easily and immediately available.

• Pre-medication prior to infusion of rituximab for RA should always be administered.

• Patients with pre-existing cardiac conditions and those who experienced prior cardiopulmonary adverse reactions need to be monitored closely following the rituximab infusion.

An analgesic/anti-pyretic (e.g. acetaminophen) and an anti-histaminic drug (e.g. diphenhydramine) should always be administered before each infusion of rituximab.

Reference:

Advisories, Warnings and Recalls, Health Canada, 2 June 2011 (www.hc-sc.gc.ca).

Risperidone and Ropinirole

Medication errors - Name confusion

USA. The US FDA notified health-care professionals and the public of medication error reports in which patients were given risperidone (Risperdal®) instead of ropinirole (Requip®) and vice versa. In some cases, patients who took the wrong medication needed to be hospitalized.

Risperidone (Risperdal®) is an antipsychotic medication used to treat mental illnesses including schizophrenia, bipolar disorder, and irritability associated with autistic disorder. Ropinirole (Requip®) is a dopamine agonist used in the treatment of Parkinson's disease and Restless Legs Syndrome.

The US FDA determined that the factors contributing to the confusion between the two products include:
• Similarities of both the brand (proprietary) and generic (established) names.
• Similarities of the container labels and carton packaging.
• Illegible handwriting on prescriptions.
• Overlapping product characteristics, such as the drug strengths, dosage forms, and dosing intervals.

The US FDA recommended that health-care professionals are reminded to clearly print or spell out the medication name on prescriptions and make certain their patients know the name of their prescribed medication and their reason for taking it.

Reference:

FDA Drug Safety Communication, US FDA 13 June 2011 (www.fda.gov).

Kenya hosts two pharmacovigilance training courses

Dr Jayesh Pandit, Head, Division of Medicines Information and Pharmacovigilance, Pharmacy and Poisons Board, Kenya

A major international project, with the full title 'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes', started in September 2009, and will run for a further 2½ years. 'Monitoring Medicines' (the project's short name) was developed by WHO and is coordinated by the Uppsala Monitoring Centre, with funds from the European Commission (Seventh Framework Programme (FP-7) of the Research Directorate). The project aims to improve patient safety both within the European Union and in other regions. The project partners represent a wide range of organizations dedicated to improving public health through the safe use of medicines.

Monitoring Medicines (MM) project partners include: WHO, the Uppsala Monitoring Centre (UMC), Copenhagen HIV Programme, Denmark; University of Ghana Medical School, Pharmacy and Poisons Board (PPB), Kenya, Centre Anti Poison et de Pharmacovigilance du Maroc, Lareb, Netherlands Pharmacovigilance Centre, Zuellig Foundation, the Philippines, Medical Products Agency, Sweden, Elliot Brown Consulting Ltd, UK and the National Patient Safety Agency, UK.

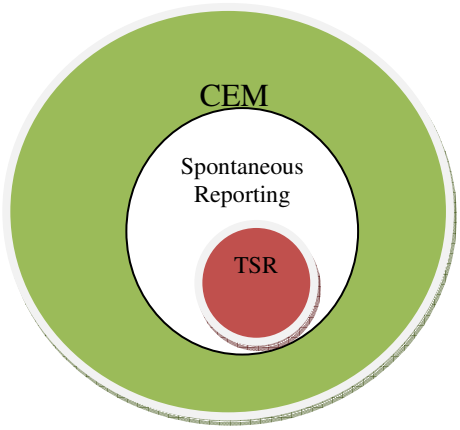
The project has four objectives:

1. Support and strengthen consumer reporting of suspected adverse drug reactions (ADRs).
2. Expand the role and scope of national pharmacovigilance centres to identify, analyse and prevent medication errors.
3. Promote better and broader use of existing pharmacovigilance data for patient safety.
4. Develop additional pharmacovigilance methods to complement data from spontaneous reporting systems.

Two training courses were organized as part of Objective 4, in Mombasa, Kenya: a training course on Cohort Event Monitoring (CEM) of antimalarial medicines, and a training course on targeted spontaneous reporting in HIV treatment programmes. The project partner from Kenya (PPB) had key responsibilities in organizing these courses.

CEM is proposed by WHO as a complement to spontaneous reporting systems when there is a need for the prospective and proactive recording of adverse events associated with one or more medicines. It is an adaptation of the New Zealand Intensive Medicines Monitoring Programme (IMMP), for monitoring a new medicine in the early post-marketing phase. The current course trained participants in applying CEM for new antimalarial medicines. Four countries attended this part of the training: Burkina Faso, Ethiopia, Kenya and Uganda.

WHO is promoting TSR within public health programmes as a best practice that improves quality of patient care. The present TSR course objective was to implement the principles of safety monitoring within an HIV treatment cohort. The training focused on introducing pharmacovigilance as a routine standard of care when treating HIV patients. Four countries were trained in this method: Botswana, Kenya, Uganda and Zimbabwe. Adverse events are captured in CEM while adverse drug reactions (ADRs) are collated through spontaneous reporting; TSR on the other hand, allows us to collect information on specific ADRs, with specific medicines, in defined cohorts. The relationship between the methods can be represented by the following figure.



The courses were hosted by the Kenyan National Pharmacovigilance Centre. Speakers included experts from the Kenyan National Pharmacovigilance Centre, WHO, the UMC, the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance in Accra, Ghana, the Copenhagen HIV Programme (CHIP) in Denmark, representatives from the Academic Model Providing Access to Healthcare (AMPATH), Eldoret, Kenya and others.

Participants from the respective work streams will now have the opportunity of developing and submitting a project proposal to WHO: two proposals (one each in CEM and TSR) will be selected for financial support from the MM project funds, to pilot the adaptation and implementation of CEM and TSR, in malaria and HIV programmes respectively.

Announcement:

A meeting 'Drugs in the environment: ecopharmacovigilance for better health' is being organized, Monday 31 October 2011, at the Royal Society of Medicine, London, to disseminate and improve knowledge on this important topic, on the link between drugs and the environment.

The full programme and registration details are available at:
http://www.rsm.ac.uk/academ/epc01.php