

# WHO PHARMACEUTICALS NEWSLETTER



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

*The aim of this 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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## **No. 5, 2007**

Three titles in this issue deserve special mention: nelfinavir, nimesulide and lumiracoxib. Nelfinavir was suspended in August 2007 in Europe when several batches of the active substance were contaminated with ethyl methanesulfonate, a known genotoxic substance. The European Medicines Agency (EMA) has now reinstated the marketing authorization in Europe, having assured itself that the contamination has been eliminated and that future productions of nelfinavir would meet the required quality standards. In May 2007 the Irish Medicines Board (IMB) announced the suspension of the marketing and sale of oral nimesulide in Ireland. (The IMB also presented nimesulide as a drug of current interest at the Thirtieth Annual Meeting of National Pharmacovigilance Centres in Buenos Aires, Argentina, in October 2007; a report from this meeting will be included in the next issue of the newsletter.) The EMA, on the other hand, has recently concluded that available data do not support a full suspension of nimesulide, thus only restricting its use. Reports of hepatotoxicity have provoked various regulatory measures for lumiracoxib: some countries have favoured its market withdrawal while others have retained the lower dose in the market.

Pharmacovigilance in resource limited settings faces several challenges, including the absence of qualified personnel. Recently, WHO organized a course for consultants in Ghana: the idea was to create a pool of pharmacovigilance experts who could provide cross-border consultancy services for pharmacovigilance in Africa. A report on the training is included.

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## **Contents**

**Regulatory matters**

**Safety of medicines**

**Feature**

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# TABLE OF CONTENTS

## Regulatory Matters

<b>Clobutinol-containing cough preparations</b> -- Withdrawn due to adverse cardiac effects .....	1
<b>Ephedrine and pseudoephedrine containing nasal decongestants</b> -- OTC products to have tighter controls .....	1
<b>Exenatide</b> -- Reports of acute pancreatitis; label to be updated .....	1
<b>Haloperidol</b> -- Labelling updated with risk of <i>torsades de pointe</i> .....	2
<b>Lumiracoxib</b> -- Risk of serious hepatotoxicity .....	2
<b>Nelfinavir</b> -- Guidance on process impurity in North America; licence re-established in Europe ...	3
<b>Nimesulide</b> -- Restricted use recommended .....	4
<b>PDE5 Inhibitors</b> -- Reports of sudden decreases in or loss of hearing .....	4
<b>Pergolide</b> -- Withdrawn in Canada .....	5
<b>Talc preparations for pleurodesis</b> -- To be treated as medicines .....	5

## Safety of Medicines

<b>Atypical antipsychotics</b> -- Not free of extrapyramidal side effects .....	6
<b>Bisphosphonates</b> -- Review of early data of atrial fibrillation .....	6
<b>Calabash chalk</b> -- May pose health risk for pregnant and breastfeeding women .....	6
<b>Colloidal silver</b> -- Health risks associated with chronic ingestion ... ..	6
<b>Duloxetine</b> -- Risk of suicidal ideation .....	7
<b>Etonogestrel</b> -- Reports of unintended pregnancy .....	7
<b>Fentanyl buccal tablets</b> -- Deaths due to improper use .....	7
<b>Lopinavir/ritonavir</b> -- Caution against accidental overdose in children .....	8
<b>Sibutramine</b> -- Contraindications to be strictly followed .....	8
<b>Zoledronic acid</b> -- Should only be given intravenously .....	9
<b>Zolpidem</b> -- Reports of sleep-walking .....	9

## Feature

<b>Report of a WHO Training Course on Pharmacovigilance for Consultants</b> .....	10
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## Clobutinol-containing cough preparations Withdrawn due to adverse cardiac effects

**Europe, Worldwide.** The European Medicines Agency (EMA) has recommended withdrawing the marketing authorization for cough medicines containing clobutinol (1). This recommendation is based on the Agency's review of the safety of clobutinol and its conclusion that the benefits of medicines containing clobutinol no longer outweigh their risks. In 2007 the German medicines regulatory authority suspended the marketing authorization for medicines containing clobutinol based on information from the manufacturer (Boehringer Ingelheim) that clobutinol was linked to adverse cardiac effects. Boehringer Ingelheim had shared the preliminary results of a study that was being performed in healthy volunteers; these results showed that the use of clobutinol led to QT-prolongation. The Committee on Medicinal Products for Human Use (CHMP) has now reviewed all available information on the safety of clobutinol and has concluded that:

- the use of clobutinol is linked to a clear risk of QT prolongation
- this risk increases when patients take higher doses of the medicine

The EMA advises that:

- patients who are currently taking clobutinol should consult their doctor or pharmacist to discuss alternative treatments;
- the risk linked to clobutinol therapy is temporary, so there is no risk in patients who have taken the medicine in the past; and
- prescription providers should not issue any new prescriptions for clobutinol.

In September 2007 Boehringer Ingelheim laboratories announced their decision to voluntarily withdraw the product (Silomat) from the global markets (2).

### References:

1. Press Release. EMA, 18 October 2007 ([www.emea.europa.eu](http://www.emea.europa.eu))
2. Letter to prescribers. AFSSAPS, 4 September 2007 (<http://agmed.sante.gouv.fr>).

## Ephedrine and pseudoephedrine containing nasal decongestants OTC products to have tighter controls

**UK.** The Medicines and Healthcare products Regulatory Agency (MHRA) has announced today that pseudoephedrine and ephedrine contained in nasal decongestants in cold and flu remedies are to have tighter controls. This follows a public consultation initiated by the MHRA as there has been an increasing concern about the potential for pseudoephedrine and ephedrine to be extracted from over-the-counter (OTC) medicines and used in the illegal manufacture of methylamphetamine (crystal meth). The CHMP has recommended that large packs of pseudoephedrine and ephedrine should be replaced by smaller packs of 720 mg (the equivalent of 12 tablets or capsules of 60 mg or 24 tablets or capsules of 30 mg) and for there to be a limit of one pack per customer. The Commission also recommended that the sale should be carried out by a pharmacist. The legal status of products containing pseudoephedrine and ephedrine should be reclassified from 'pharmacy only' to 'prescription only' (POM) in 24 months time (2009) or earlier if necessary, unless the risk of the misuse of these OTC medicines in the

illicit manufacture of methylamphetamine is contained by the measures outlined.

### Reference:

Press Release. MHRA, 29 August 2007 ([www.mhra.gov.uk](http://www.mhra.gov.uk)).

## Exenatide Reports of acute pancreatitis; label to be updated

**USA.** The United States Food and Drug Administration (US FDA) is advising that some postmarketing reports suggest an association between acute pancreatitis and exenatide (Byetta) use. Exenatide is the first of a new class of medications (incretin mimics) approved in the treatment of type 2 diabetes. It is used as an injection (s.c), with either sulfonylureas, metformin or with thiazolidinediones and increases insulin synthesis and secretion in the presence of glucose. The US FDA has reviewed 30 postmarketing reports of acute pancreatitis in patients treated with exenatide (Byetta), 27 of the 30 patients had at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridaemia, and alcohol use. In six patients the symptoms of pancreatitis began or worsened soon after the dose of exenatide was increased from 5 micrograms twice daily to 10 micrograms twice daily. Twenty-one patients were hospitalized. There were no reports of hemorrhagic or necrotizing pancreatitis. However, five patients developed serious complications including dehydration and renal failure; suspected ileus; phlegmon; and ascites. Twenty-two of the 30 reports indicated that the patients improved after discontinuing exenatide (Byetta).

Details in three reports indicated that the symptoms of acute pancreatitis returned when exenatide was restarted. Nausea and vomiting returned in two patients when exenatide was restarted. In a third patient, abdominal pain returned when exenatide was restarted and abated after exenatide was permanently discontinued.

The Agency advises health-care professionals to instruct patients taking exenatide to seek prompt medical care if they experience unexplained persistent severe abdominal pain which may or may not be accompanied by vomiting. If pancreatitis is suspected, exenatide should be discontinued. If pancreatitis is confirmed, exenatide should not be restarted unless an alternative etiology is identified.

The US FDA has asked the manufacturer (Amylin Pharmaceuticals, Inc) to include information about acute pancreatitis in the Precautions section of the product label.

**Reference:**

Information for health-care professionals. US FDA, 16 October 2007 ([www.fda.gov](http://www.fda.gov)).

## Haloperidol

### Labelling updated with risk of *torsade de pointes*

**USA.** The US FDA has advised that the labelling for haloperidol, (Haldol, Haldol Decanoate, and Haldol Lactate) has been revised with regard to the risk of *torsades de pointe* and QT prolongation in patients treated with the drug. The Agency explains that the labelling changes have been prompted by a number of case reports of sudden death, *torsades de pointe* and QT prolongation in patients who have received treatment with haloperidol, especially when administered intravenously or at higher than recommended doses. The updated Warnings section states that higher doses and intravenous

administration of haloperidol appear to be linked with a higher risk of *torsades de pointe* and QT prolongation. Particular caution is recommended in patients who have other QT-prolonging conditions (such as electrolyte imbalance), underlying cardiac abnormalities, hypothyroidism or familial long QT syndrome, or who are receiving drugs known to prolong QT interval. ECG monitoring is recommended if haloperidol is administered IV. The Warnings section also states that haloperidol is not approved for intravenous administration.

**Reports in WHO database:**

Haloperidol

QT prolonged - 57

*Torsades de pointe* - 62

Haloperidol decanoate

QT prolonged - 3

*Torsades de pointe* - 1

Haloperidol lactate

QT prolonged - 1

**Reference:**

Information for health-care professionals. US FDA, September 2007 ([www.fda.gov](http://www.fda.gov)).

## Lumiracoxib

### Risk of serious hepatotoxicity

Lumiracoxib (Prexige), is a COX-2 selective non-steroidal anti-inflammatory drug (NSAID) used to treat painful symptoms of osteoarthritis of the knee and hip at a dose of 100 mg once daily. It is approved in more than 50 countries worldwide and was first launched in Brazil in 2005. Concern was raised worldwide after rare reports of serious liver reactions, mostly relating to daily doses that were higher than licensed for use in osteoarthritis. Some post-marketing reports of severe hepatic adverse effects have been reported in some countries around the world. Some countries have reacted

with specific regulatory measures:

**Australia (1).** In August 2007 Australia's Therapeutic Goods Administration (TGA) cancelled the registration of lumiracoxib due to reports of serious liver adverse effects associated with the use of the drug. As of 10 August this year, the TGA had received eight reports of serious liver adverse reactions related to lumiracoxib, including two deaths and two liver transplants. These reports were "urgently investigated" by the TGA and its expert advisory committee, the Adverse Drug Reactions Advisory Committee (ADRAC). ADRAC subsequently recommended the cancellation of registration for lumiracoxib, "due to the severity of the reported side effects associated with this drug". The TGA is advising patients to discontinue lumiracoxib use immediately, and to discuss alternative treatments with their physician.

**Canada (2).** Health Canada has reviewed all safety and efficacy data for lumiracoxib from Novartis and has concluded that the risk of serious hepatotoxicity associated with the use of lumiracoxib cannot be safely and effectively managed. Health Canada has thus requested that Novartis stop the sale of lumiracoxib in Canada. Consistent with this decision to cease sales and marketing of lumiracoxib, Novartis is asking Canadian pharmacists and distributors to return the product to the company. Patients taking lumiracoxib have been advised to discontinue its intake and contact their physician for advice about alternative therapies.

Prescribers are advised: not to initiate treatment of new patients; to advise patients to discontinue lumiracoxib;

to review treatment options for patients currently taking lumiracoxib.

Pharmacists are advised: not to dispense further prescriptions for lumiracoxib; to tell patients to discontinue lumiracoxib and contact their physician if they have any concerns.

Consumers are advised to return the product to their pharmacy.

**New Zealand (3).** The regulatory agency has withdrawn the market authorization for 200 mg and 400 mg lumiracoxib tablets for acute use, but kept the licenses of 100 mg once daily for osteoarthritis.

**Turkey (3).** Turkey has suspended the marketing authorization for 100 mg lumiracoxib tablets pending further review.

**United Kingdom (3).** Concern was raised worldwide after rare reports of serious liver reactions mostly relating to daily doses of lumiracoxib that are higher than licensed in the EU. Following consultation with the MHRA and other European regulators, the manufacturer of the osteoarthritis drug, lumiracoxib (Prexige), has written to health professionals to inform them of new restrictions on the prescribing of lumiracoxib.

A summary of the latest advice from MHRA includes the following: Lumiracoxib should not be used in patients with current or past liver disease, those taking other medicines that may cause liver problems, or who have had previous drug-induced liver reactions. Blood tests to check liver function are needed before treatment, at monthly intervals during treatment, and at any stage if patients are unwell with possible liver problems. Patients already taking lumiracoxib should have their treatment reviewed at the next convenient opportunity. Blood tests should be taken if

continued treatment is considered appropriate. Do not exceed 100 mg once daily and use only for the shortest duration necessary to control symptoms.

**Reports in WHO database:**  
*Hepatic function abnormal - 3*

**Reference:**

1. *Media Statement. Therapeutics Goods Administration, 11 August 2007* ([www.tga.gov.au](http://www.tga.gov.au))
2. *'Dear Health-care Professional' letter from Novartis Pharmaceuticals Canada Inc. 3 October 2007* ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))
3. *Lumiracoxib and liver adverse reactions: MHRA, updated 24 October 2007* ([www.mhra.gov.uk](http://www.mhra.gov.uk))

## Nelfinavir Guidance on process impurity in North America; licence re-established in Europe

**Canada (1).** Pfizer in consultation with Health Canada has notified health professionals about the presence of low levels of ethyl methanesulfonate (EMS), a process-related impurity in nelfinavir (Viracept) and has provided guidance on the use of nelfinavir (Viracept) in patients, including pregnant women and paediatric patients. Nelfinavir was removed by Roche Limited from the European market in June 2007 (see WHO Pharmaceuticals Newsletter No. 3, 2007), due to detection of high levels of EMS in some products there. In the Canadian product (manufacturing source is different from that of the European formulations), the level of exposure is over 200 times less than that found in Europe.

EMS is a potential human carcinogen. Data from animal studies indicate that EMS is teratogenic, mutagenic and

carcinogenic. However, no data from humans exist. Animal studies do not necessarily predict human risk. Pfizer advises that at this time, physicians should consider the risks and benefits of prescribing nelfinavir to their HIV-infected adult patients.

In general, Health Canada recommends that HIV-infected patients should be switched from nelfinavir to an alternative therapy if this can be done safely. Health-care professionals are requested to facilitate access for these patients. However, patients should NOT stop taking nelfinavir without first consulting with their physician. Pregnant women and children may be more susceptible to harm from EMS and should be switched to alternative therapy as soon as medically feasible. Nelfinavir should NOT be prescribed for adults and children needing to initiate therapy. Pharmacists should notify the treating HIV physician when patients request for renewal of nelfinavir prescriptions. Patients taking nelfinavir should contact their physician for discussion of whether they should continue or be switched to other treatments. For patients without other reasonable treatment options, Health Canada and Pfizer agree that there remains a positive benefit/risk for continued use of nelfinavir.

The levels currently deemed acceptable for long-term exposure to EMS suggest a theoretical lifetime increased cancer risk in adults of less than one case per 100 000 patients exposed. While no data on the impact of high EMS levels in humans exist, estimates from in-vitro and animal data suggest that currently observed EMS levels in Canadian formulations may result in cancer risk in adults between 1 and 17 cases per 100 000 patients exposed for a lifetime. Current estimates of

the background incidence of cancer in the HIV population are about 20 to 30 cases per 1000 patient-years. Pfizer is working with Health Canada to prospectively limit EMS levels in nelfinavir while still considering the immediate needs of patients on therapy. Further relevant information will be provided as it becomes available.

**USA (2).** Pfizer has issued a 'Dear Health-care Professional' letter regarding the presence of process-related EMS in nelfinavir (Viracept) 250 mg and 625 mg tablets and in nelfinavir powder for oral suspension in the USA. The letter was prompted by detection of excess levels of EMS in Roche-manufactured nelfinavir in June 2007; the US FDA and Pfizer have agreed new limits for EMS in Pfizer-manufactured nelfinavir marketed in the US. Testing showed that the levels of EMS were substantially lower than those that led to the Roche recall. At this point, Pfizer advises that paediatric patients and pregnant women starting HIV therapy should not receive regimens containing nelfinavir. The US FDA and Pfizer determined that the benefit-risk ratio remains favourable for paediatric patients who are stable on nelfinavir-based regimens and that they should continue to receive nelfinavir. Pregnant women should be switched from nelfinavir to an alternative antiretroviral therapy while progress is made towards the long-term EMS specification. However, for those women with no alternative therapy options, the US FDA and Pfizer agree that the risk-benefit ratio for continuing nelfinavir remains favourable.

**Europe (3).** The marketing authorization for nelfinavir was suspended on 6 August 2007 in Europe during the manufacturing process of several batches of the active substance with EMS. The European Medicines Agency's Committee on Medicinal Products for Human Use (CHMP) has subsequently evaluated the corrective and preventive measures put in place by Roche,

the manufacturer of nelfinavir in Europe. The CHMP is reassured that the cause of the contamination has been eliminated and that future productions of nelfinavir would meet the required quality standards. The CHMP has therefore recommended lifting of the suspension of the marketing authorization for nelfinavir in Europe. Roche intends to re-supply nelfinavir as soon as possible. Roche has advised that the timing of the re-introduction will vary from country to country and it is likely to be a few months before it is fully available to prescribers and patients.

**Reference:**

1. 'Dear Health-care Professional' letter from Pfizer Canada Inc. 10 September 2007 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))
2. 'Dear Health-care Professional' letter from Pfizer Inc. 10 September 2007 ([www.fda.gov](http://www.fda.gov))
3. Press Release. EMEA, 20 September 2007 ([www.emea.europa.eu](http://www.emea.europa.eu))

## Nimesulide Restricted use recommended

**Europe.** The EMEA has completed a review of liver safety data for nimesulide-containing medicinal products. The Agency advises that the benefits of these medicines still outweigh their risks but recommends restricting the duration of use of nimesulide-containing medicinal products to minimize the risk of liver injury. The EMEA's CHMP stated that the available data do not support suspension of all marketing authorizations in Europe. However, it also concluded that marketing authorizations need to be changed, and the current information to physicians and patients should be amended to restrict the risk of liver damage.

(In May 2007, the Irish Medicines Board announced the suspension of the marketing and sale of oral nimesulide in Ireland. WHO issued an Information Exchange System Alert with this information; see WHO Pharmaceuticals Newsletter No. 3, 2007).

**Reference:**

*Questions and answers on the CHMP recommendation on nimesulide-containing medicines.* EMEA, 21 September 2007 ([www.emea.europa.eu](http://www.emea.europa.eu))

## PDE5 Inhibitors Reports of sudden decreases in or loss of hearing

**USA.** The US FDA informed health-care professionals of reports of sudden decrease in, or loss of hearing following the use of phosphodiesterase type 5 enzyme (PDE5) inhibitors sildenafil (Viagra), vardenafil (Levitra), tadalafil (Cialis) for the treatment of erectile dysfunction, and sildenafil citrate (Revatio) for the treatment of pulmonary arterial hypertension. In some cases, the sudden hearing loss was accompanied by tinnitus and dizziness. Medical follow-up on these reports was often limited, which makes it difficult to determine if the loss of hearing was related to the use of one of the drugs, an underlying medical condition or other risk factors for hearing loss, a combination of these factors or other factors. The PRECAUTIONS and ADVERSE REACTIONS sections of the approved product labelling for Viagra, Levitra, and Cialis were revised. FDA is working with the manufacturer to revise the labelling for Revatio.

**Reference:**

*Health-care Professional Information.* US FDA, 10 October 2007 ([www.fda.gov](http://www.fda.gov)).

## Pergolide Withdrawn in Canada

**Canada.** Eli Lilly has stopped sales of pergolide [Permax] in Canada as of 30 August 2007. According to Eli Lilly, there is now sufficient evidence of valvulopathy in pergolide recipients. The company has advised health-care professionals to gradually switch pergolide recipients to an alternative therapy for Parkinson's disease at the earliest possible point, and not to start pergolide treatment in new patients. Pergolide should be gradually reduced over several weeks to prevent serious adverse events associated with abrupt discontinuation and recurrence of symptoms of the underlying condition; abrupt discontinuation of pergolide can lead to adverse events like hallucinations, neuroleptic malignant syndrome-like symptoms and confusion. Eli Lilly has advised patients not to stop pergolide on their own and to contact their health-care provider as soon as possible to discuss alternative treatment options. (See WHO Pharmaceuticals Newsletter No. 2, 2007 for previous voluntary decisions to withdraw pergolide by manufacturers).

**Reference:**

*'Dear Health-care Professional' letter from Eli Lilly Canada Inc. August 2007*  
([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).

## Talc preparations for pleurodesis To be treated as medicines

**United Kingdom.** The MHRA has stated that talc preparations for pleurodesis are to be treated as medicinal products because they promote an inflammatory reaction in the local tissues through a metabolic/ immunological response after exposure to the talc. MHRA therefore considers

that these are not medical devices and intends to treat these products as medicines that will require a manufacturing authorization from 1 January 2008. However, in the interim period, since there are no licensed talc preparations for pleurodesis, these products may be prescribed by health-care professionals as unlicensed medicines for the special clinical needs of individual patients at the direct personal responsibility of the prescriber.

**Reference:**

*Drug Alert. MHRA, 10 October 2007*  
([www.mhra.gov.uk](http://www.mhra.gov.uk)).

## Atypical antipsychotics

### Not free of extrapyramidal side effects

**Australia.** According to the Australian Adverse Drug Reactions Advisory Committee (ADRAC) atypical antipsychotics may have a lower propensity for causing extrapyramidal side effects (EPS) when compared with typical antipsychotics, but they are not devoid of EPS. In the ADRAC database there is a lower incidence of EPS with atypical antipsychotics, compared with haloperidol (see [Table 1](#)). However, the agency has called for caution when interpreting these results as reports with atypical antipsychotics may be confounded by previous exposure to typical antipsychotics.

Reports of EPS with antipsychotics		
	EPS reports	Total reports
Aripiprazole	33	147
Risperidone	159	812
Quetiapine	42	315
Olanzapine	129	1203
Clozapine	70	3775
Haloperidol	321	753

**Table 1.** Reports of EPS with antipsychotics

The most common adverse reactions reported include dystonia, dyskinesia, akathisia and other non-specified extrapyramidal disorders. About one-third of the patients had not recovered at the time of reporting.

**Reference:**  
*Australian Adverse Drug Reactions Bulletin 26(4): 15 August 2007.*

## Bisphosphonates

### Review of early data of atrial fibrillation

**USA.** The US FDA has issued an 'Early Communication' of its ongoing safety review about association between bisphosphonate use and atrial fibrillation (AF).

Bisphosphonates are a class of drugs used primarily to increase bone mass and reduce the risk for fracture in patients with osteoporosis, slow bone turnover, Paget's disease of the bone, to treat bone metastases, and lower elevated levels of blood calcium in patients with cancer. The FDA says that these early data are difficult to interpret, as many of the patients in the studies were aged over 65 years, and AF is common in this patient group. The Agency will conduct an in-depth evaluation of the association between bisphosphonate use and AF, and monitor postmarketing AF reports in bisphosphonate recipients. Patients or health-care providers need not change their bisphosphonate treatment at this stage.

**Reference:**  
*Early communication of an ongoing safety review. US FDA, 1 October 2007.*  
([www.fda.gov](http://www.fda.gov)).

## Calabash chalk

### May pose health risk for pregnant and breastfeeding women

**Canada.** Health Canada has issued an 'Advisory' to warn Canadians not to use Calabash chalk, especially women who are pregnant or breast-feeding; testing of the chalk showed that it contained arsenic and high levels of lead, both of which have been associated with adverse effects. Calabash chalk, which is generally sold loose, is not authorized for sale in Canada, but is used by some

pregnant women for the alleviation of morning sickness. The Agency warns that, following lead exposure, the developing child is at particular risk of adverse effects on the nervous system and neurological development, and that adverse effects associated with excessive long-term arsenic exposure include urinary, bladder, skin and lung cancers.

**Reference:**  
*Advisory. Health Canada, 2 October 2007*  
([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

## Colloidal silver

### Health risks associated with chronic ingestion

**Australia.** ADRAC has received four reports of silver toxicity (argyria) following ingestion of homemade products containing colloidal silver (tiny particles of metallic silver suspended in liquid) prepared using a "colloidal silver generator":

- A five-year old boy who ingested colloidal silver daily for several months developed grey discoloration of skin and tongue and abnormal hepatic function.
- An elderly man who drank colloidal silver daily for six months required hospital admission for debilitating fatigue accompanied by blue skin discoloration, dilated cardiomyopathy, amnesia and incoherent speech.
- An elderly man consuming liquid made using a "colloidal silver generator" over a four-year period developed grey skin discoloration.
- An adult male ingesting homemade colloidal silver daily for three years and also applying it topically after shaving developed generalized skin discoloration.

There are no products containing colloidal silver

approved for marketing in Australia. The ADRAC cautions that with the exception of registered topical silver preparations, there is no evidence to support the safety or efficacy of silver regardless of its form or method of manufacture; and that silver has no known nutritional benefit and its well-defined toxicity can occur with all forms of the metal, including silver salts and colloids.

Argyria is the main toxicity associated with chronic ingestion or topical absorption of silver, including colloidal forms of silver. It is characterized by an irreversible, generalized blue-grey discoloration of the subepithelial layer of skin. Later, the entire skin, deep tissues, mucous membranes, nails, conjunctiva, cornea, and lens may be affected. Argyria discoloration may be misdiagnosed as cyanosis, methaemoglobinemia or haemochromatosis. Other toxicities associated with ingested silver may include peripheral neuropathies, seizures, and haematological, cardiac, hepatic and nephrotoxic derangements. ADRAC has received no reports of argyria associated with legitimate therapeutic goods containing presentations of silver that remain appropriate, for example, topical silver nitrate for neonatal conjunctivitis or silver sulfadiazine for burns.

#### Reference

*Australian Adverse Drug Reactions Bulletin 26(5): 19, October 2007*

## Duloxetine

### Risk of suicidal ideation

**UK.** Cases of suicidal ideation and suicidal behaviour have been reported in the UK among patients receiving treatment with duloxetine, or shortly after stopping treatment. Duloxetine is marketed as Cymbalta for the

treatment of major depressive disorder and diabetic neuropathy, and as Yentreve for the treatment of stress urinary incontinence. The MHRA advises that the different preparations of duloxetine (Cymbalta and Yentreve):

- should be prescribed for their intended use, and should not be prescribed together
- should not be prescribed to patients with severe kidney impairment, liver disease leading to impaired liver function, or uncontrolled hypertension
- should not be withdrawn abruptly

The benefit of taking duloxetine (Yentreve) for stress urinary incontinence should be assessed regularly; the benefit of taking duloxetine (Cymbalta) for diabetic neuropathy should be assessed at least every three months. Cymbalta or Yentreve should not be prescribed to patients receiving nonselective, irreversible monoamine oxidase inhibitors for depression, fluvoxamine for depression or obsessive compulsive disorder, or ciprofloxacin. Moreover, Cymbalta should be used with caution alongside other antidepressants or St. John's Wort, and Yentreve is not recommended for use in combination with antidepressants.

#### Reports in WHO database:

Duloxetine  
Suicide attempt - 157 since 2005

#### Reference:

*Drug Safety Update 1(2):11, September 2007*  
([www.mhra.gov.uk](http://www.mhra.gov.uk)).

## Etonogestrel

### Reports of unintended pregnancy

**Australia.** Since 2001, ADRAC has received 32 reports of unintended pregnancy in etonogestrel (Implanon) recipients due to a suspected interaction with carbamazepine (26 reports), phenytoin (4), methylphenobarbital (1) and rifampicin. Unintended pregnancies were attributed to reduced plasma concentrations of etonogestrel due to a potent induction of CYP3A4 and other phase I and phase II liver enzyme systems by the interacting medicines; etonogestrel is catalysed by CYP3A4. According to ADRAC, interaction between etonogestrel and other medicines like primidone, oxcarbazepine, rifabutin, griseofulvin and hypericum (St John's Wort) can possibly reduce the contraceptive effect of etonogestrel or lead to haemorrhage. The Agency has advised prescribers to replace etonogestrel with a non-hormonal, contraceptive method in women receiving long-term treatment with hepatic enzyme-inducing medicines.

#### Reports in WHO database:

Pregnancy unintended - 720 (since 2001)

#### Reference:

*Australian Adverse Drug Reactions Bulletin 26(4): 14-15 August 2007.*

## Fentanyl buccal tablets

### Deaths due to improper use

**USA.** The US FDA issued a 'Public Health Advisory' and a 'Health-Care Professional Sheet' to alert health-care professionals and consumers regarding concerns over the use of fentanyl buccal tablets (Fentora) after recent reports of deaths and other adverse events. Fentanyl buccal tablets are used to treat moderate-to-severe sudden (breakthrough)

cancer pain. The Agency advises that the deaths reported were the result of improper selection of patients, dosing, or improper product substitution.

The US FDA has warned physicians and other health-care professionals that it is critical to follow product labelling when administering fentanyl buccal tablets. US FDA has further stated that it is dangerous to use this product (Fentora) for any short-term pain such as headaches or migraines; or in patients who are not opioid tolerant. Patients also must be under a doctor's care and close supervision while taking fentanyl buccal tablets and the dose should be carefully adjusted to control breakthrough pain adequately.

In addition, the US FDA is concerned about the improper substitution of fentanyl buccal tablets (Fentora), a quick acting pain drug, for other pain medicines. Fentora is not the same as other fentanyl products and cannot be substituted for Actiq, another fentanyl product used to treat breakthrough cancer pain. Because Fentora delivers more fentanyl to the blood than Actiq, substituting Fentora for Actiq using the same dose can result in a fatal overdose.

**Reference:**

*Public Health Advisory. US FDA, 26 September 2007*  
([www.fda.gov](http://www.fda.gov)).

## Lopinavir/ ritonavir Caution against accidental overdose in children

**Netherlands, UK.** Abbott has issued a 'Dear Health-care Professional' letter advising that the company has been notified of a fatal accidental overdose of lopinavir/ritonavir (Kaletra) in a 44-days-old infant. The infant, who had been born at 30

weeks' gestation with HIV infection, received about 6.5ml of lopinavir/ritonavir (Kaletra) oral solution (approximately 10 times the calculated volume) and, nine days later, the infant died of cardiogenic shock. Abbott reminds health-care professionals that lopinavir/ritonavir (Kaletra) Oral Solution is highly concentrated, and contains lopinavir/ritonavir 80 mg/20 mg per ml, not per bottle. The company advises that dosages of the oral solution are calculated based on body surface area for children, and that children should receive less than 5ml per dose unless they are also receiving efavirenz or nevirapine, antiretrovirals known to lower the plasma concentration of lopinavir/ritonavir. Abbott asks that reference is made to the prescribing information for dosing recommendations in children, and that health-care professionals make patients, their caretakers and staff aware that care is needed when giving lopinavir/ritonavir (Kaletra) oral solution to children.

**References:**

1. 'Dear Health-care Professional' letter from Abbott Laboratories Ltd. UK, 3 August 2007  
([www.mhra.gov.uk](http://www.mhra.gov.uk))
2. Direct Health-care Professional Communications (DHPC) in the Netherlands from Abbott on Kaletra, 6 August 2007  
([www.cbg-meb.nl/](http://www.cbg-meb.nl/))

## Sibutramine Contraindications to be strictly followed

**Canada.** Sibutramine (Meridia), a serotonin and norepinephrine reuptake inhibitor, is an antiobesity agent marketed in Canada since February 2001. Sibutramine is indicated as adjunctive therapy within a weight management programme for obese patients with an initial body mass index (BMI) of 30 kg/m<sup>2</sup> or higher,

and for obese patients with an initial BMI of 27 kg/m<sup>2</sup> or higher in the presence of other risk factors (e.g., controlled hypertension, type 2 diabetes, dyslipidaemia, visceral fat). The Canadian product monograph of sibutramine includes several contraindications. Non-compliance with contraindications could result in serious adverse reactions. A history of coronary artery disease, congestive heart failure, arrhythmias or cerebrovascular disease (stroke or transient ischaemic attack), inadequately controlled or unstable hypertension, psychiatric illness, concomitant use of centrally acting drugs or herbal remedies (e.g., St John's Wort) for the treatment of psychiatric disorders and anorexia nervosa are some of the contraindications for sibutramine.

From 1 January 2001 to 31 May 2007, Health Canada received 65 reports of cardiovascular adverse reactions suspected of being associated with sibutramine. Thirteen of these reports involved patients with at least one contraindicated condition. For example, a patient with a history of myocardial infarction (MI) who was taking fluoxetine experienced fatal ventricular fibrillation two days after starting sibutramine therapy. A patient with a history of MI experienced a non ST-segment elevation MI 21 days after starting sibutramine therapy. Three patients experienced serotonin syndrome, with cardiovascular adverse reactions (e.g., hypertension, palpitation and tachycardia), from the concomitant use of a selective serotonin reuptake inhibitor (SSRI) and sibutramine. One patient, who experienced unstable hypertension after surgery, resumed her preoperative regimen of sibutramine two days after surgery and experienced worsening hypertension, headache and cerebral oedema. In this case,

meperidine was reported as a co-suspect drug. One patient experienced a vitreous haemorrhage approximately 10 days after starting sibutramine therapy. In this case, paroxetine and bupropion were stopped one day before sibutramine was started. In 2002 and 2003, international regulatory actions were taken, including safety notices, concerning cardiovascular adverse reactions associated with sibutramine. Health Canada and other foreign regulatory agencies reviewed the safety of sibutramine and concluded that the benefit-risk profile of sibutramine remained favourable. Contraindications to the use of sibutramine are well detailed in the Canadian product monograph. Health Canada continues to monitor adverse reactions suspected of being associated with sibutramine.

The Agency advises that before starting treatment with sibutramine, health professionals should review its labelled contraindications in the product monograph; consumers should consult the consumer information leaflet provided in the original packaging, particularly the section "When it should not be used".

**Reference:**

*Advisories and Warnings.*  
Health Canada, 2007  
([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

## Zoledronic acid Should only be given intravenously

**Australia.** Renal adverse effects are reported in 31 of the 268 individual case safety reports for zoledronic acid (Zometa) in Australia. The 31 reports describe either renal failure (16) or renal impairment (15). Zoledronic acid is a bisphosphonate used to treat high levels of calcium in the blood that may be caused by certain types of cancer. Zoledronic acid is also used along with cancer

chemotherapy to treat bone damage caused by multiple myeloma. It comes as a solution to be infused intravenously over at least 15 minutes. There is a well-known risk of deterioration in renal function with intravenous bisphosphonates administered at a rapid infusion rate. ADRAC notes that while the deterioration in renal function with zoledronic acid (Zometa) was usually acute, in many of the 31 cases it did not appear to be related to a rapid infusion rate. Zoledronic acid was the only suspected drug in 20 of the 31 reports. Interstitial nephritis was described in three. Ages ranged from 44 to 88 years (median 63 years). Time to onset in about two thirds of the reports was between one and three months after starting zoledronic acid. Recovery was mostly unknown or unspecified. Zoledronic acid was being used for a variety of indications with multiple myeloma (13 cases), the most common, but also breast cancer (5), prostate cancer (4), plasmacytoma, malignant melanoma, osteoporosis, bone metastases and osteomyelitis (one case each). Only four reports did not specify the reason for use. Many of the reports described patients with pre-existing renal impairment. The product information (for Zometa) includes comprehensive information on the need to monitor renal function and use in patients with pre-existing renal impairment. It also provides detailed information on risk factors for renal adverse events which include dehydration, pre-existing renal impairment, multiple cycles of bisphosphonates, as well as the use of other nephrotoxic drugs, or using an infusion time shorter than 15 minutes. Renal impairment and renal failure are both mentioned under Adverse Reactions as common (1-10%) and uncommon (0.1-1%) respectively. ADRAC reminds prescribers of bisphosphonates to pay close

attention to risk factors for renal impairment and to adhere strictly to the instructions for use.

**Reference:**

*Australian Adverse Drug Reactions Bulletin* 26(5): 18, October 2007

## Zolpidem Reports of sleep- walking

**Singapore.** Singapore's Health Sciences Authority has received four reports of unusual sleep-related disorders in patients receiving zolpidem. The four cases involve women aged 40-76 years who had been receiving zolpidem for 22-68 days prior to symptom onset. Two women experienced abnormal sleep-related events, one developed amnesia with a "dream-like state" and the other began sleep walking. The women were receiving zolpidem at dosages higher than recommended, which may have contributed to the occurrence of abnormal sleep-related events. Confounding factors such as concomitant drugs made assessment of causality difficult; however, an association between these events and zolpidem could not be excluded. (Australia has records of similar reports; see WHO Pharmaceuticals Newsletter No. 2, 2007).

**Reports in WHO database:**

Amnesia- 678  
Sleep disorder- 102  
Somnambulism- 66

**Reference:**

*Adverse Drug Reaction News (Singapore)* 9(2): 3 August 2007.

**Report of a WHO Training Course on Pharmacovigilance for Consultants**

Accra, Ghana, 2-6 July 2007-11-02

**Executive summary**

There is an urgent need to develop responsible and operative systems for pharmacovigilance in resource-limited countries to assure efficient collection and assessment of drug safety data particularly from new drugs being used in public health programmes. Concerted efforts should therefore be made to ensure that such systems are available and working. The Consultants' training course on pharmacovigilance was held with the objective of training a pool of expert pharmacovigilantes to be able to provide consultancy services on the establishment and effective operation of pharmacovigilance systems in public health programmes in Africa. The ultimate aim is to build capacity in pharmacovigilance in countries throughout Africa. The present course should be used as a template for future courses.

**Background**

Development of pharmacovigilance in resource poor settings of Africa faces several challenges. The biggest challenge is the acute lack of resources and political commitment resulting in a lack of qualified personnel to carry out pharmacovigilance work. Other problems include poor communication facilities, unbridled and uncontrolled supply of medicines and absence of functional national drug regulatory authorities. Pharmacovigilance is a relatively underdeveloped activity, in Africa with only 10 countries having national centres participating fully in the WHO Programme for International Drug Monitoring, a further 11 are associate members. These 21 countries of which 17 are in sub-Saharan Africa, are at various levels of development and activity and their overall contribution in terms of reports to the global pharmacovigilance database is small. However, there are encouraging developments including the increasing collaboration between pharmacovigilance and public health programmes.

The integration of pharmacovigilance into public health programmes has the advantages that public health programmes are relatively well funded, circumscribed and provide a perfect setting for the treatment and follow-up of patients, most of whom are able to return to the treating practitioner for assessment of any unwanted adverse events. Some of the chemotherapeutic interventions in public health programmes are community-based and it is possible to obtain good quality adverse drug reaction reports from auxiliary health workers as shown by the successful pharmacovigilance programme linked to the intermittent preventive treatment of pregnant women with sulfadoxine pyrimethamine in Ghana. Collaboration between pharmacovigilance and public health programmes is an opportunity to rationalize the limited resources in poor countries. It is also suggested that Pharmacovigilance Centres in resource limited countries should include intensive cohort event monitoring of specific medicines and that, in the absence of a Pharmacovigilance Centre, a Cohort Event Monitoring (CEM) programme could be undertaken on medicines that are vital in public health programmes.

Presentations were made by all the countries represented. They demonstrated the vast differences in the stages of development of pharmacovigilance in the countries represented. A series of sessions were convened on various difficult topics including: root cause analysis, treatment strategies, complex issues in pharmacovigilance, crisis and communication issues, cohort event monitoring, networking, quality issues and database issues. General recommendations and action points from each of the sessions were developed.

**General recommendations were as follows:**

## 1. Country specific

- Advocacy at all levels to promote Pharmacovigilance and obtain necessary political and financial support is required. This can be promoted by each country preparing a briefing note for policy makers and health managers.
- Pharmacovigilance capacity should be strengthened and shared both within and across countries.
- Countries should take responsibility for all medicine-related issues in their jurisdiction.
- Pharmacovigilance should be integrated into all public health programmes at national level.
- Cohort event monitoring should be considered an integral part of pharmacovigilance.
- Pharmacovigilance should include the safety monitoring of traditional and alternative medicines.
- Pharmacovigilance should be a part of basic and continuing health education.
- A comprehensive textbook on pharmacovigilance for Africa should be developed.

## 2. WHO specific

- Advocacy at all levels to promote pharmacovigilance and obtain necessary political and financial support is required. This can be promoted by WHO preparing briefing notes for WHO Representatives (WRs), Global Fund and other donors.
- All WHO public health programmes should introduce pharmacovigilance into their training programme.
- WHO should update recommendations concerning the use of medicines as required. The impact of the policies should be evaluated.
- WHO should undertake to evaluate National Pharmacovigilance Centres.
- WHO should continue to encourage Pharmacovigilance as an integral part of the concept of rational use of medicines.

### Treatment Strategies

A presentation was made by the malaria programme in AFRO which stimulated much discussion. The presentation concentrated on treatment strategies in malaria but the recommendations could be extrapolated to other diseases. It was stressed that in implementing a strategy consensus building and selection of options among policy makers, control programmes, stakeholders, and researchers was important. Having a supervisory body to oversee the development, implementation and revision of policy was also emphasized. The problems that were identified included insufficient evidence to define and develop consensus on the local problem and best solution; limited information gathered by monitoring and evaluation of the existing policy and policies in other countries; solutions not being articulated clearly for decision makers.

An in-depth discussion followed this presentation and the following action points were identified:

- Data on adherence are urgently needed since poor adherence may lead to resistance;
- It is recommended that a risk management plan is put in place whenever new medicines (artemisin-based combination therapies, ACTs, in particular) are registered in a country. Collaboration should be facilitated between the malaria, HIV/AIDS, TB and pharmacovigilance programmes if possible by the focal person at the WHO country office.
- Specific research is needed on understanding interactions between medicines used in malaria, HIV/AIDS and TB; interactions with alternative medicines; and addressing issue of dermatological reactions with sulfa-containing medicines;
- Pregnant and breastfeeding women exposed to new medicines should be monitored for any adverse events and pregnancy outcome;
- Pharmaceutical industries manufacturing antimalarials and antiretrovirals should be encouraged to apply for WHO prequalification.

### Crisis and Communication issues

A tutorial was held on communication and issues pertaining to crises. One of the major messages from the communications session was that the core process is an active, open two-way communication. The main conclusions from the crisis management session were: some crises can be prevented by careful review of current vulnerabilities and risk assessment. The impact of unexpected crises can be greatly reduced by careful planning. The action points from these two sessions were as follows:

- Standard Operating Procedures should be developed for medicinal product crisis management.
- A medicinal product crisis requires good information to deal with it and should be treated like a drug-safety signal and include the following actions
  - Search WHO database
  - Pose query on Vigimed
  - Perform a root cause analysis
- The influence of non-medicinal factors (e.g. system errors) should be properly understood.
- A compilation of critical crises cases should be developed.
- A web site (blog) should be created for sharing experience in crisis management and communication.
- More time should be allocated to communication issues in training courses.
- A communication guideline and materials on pharmacovigilance issues should be developed.
- The WHO Information Exchange Alert format could be used as a template for communicating any crisis.

### Cohort Event Monitoring (CEM)

An overview of the methodology of CEM was presented. (For further details on the methodology please refer to the Practical Handbook on the Pharmacovigilance of antimalarial medicines, in press, and the publication "Pharmacovigilance for antiretrovirals in resource-poor countries" (see under recent publications at [www.who.int/medicines/publications/](http://www.who.int/medicines/publications/))). It was agreed that this method was one of the most suitable for collecting data on new medicines introduced into African countries. Action points from this session:

- Include CEM in public health programmes as good pharmacovigilance practice.
- New medicines for use in public health programmes as well as old medicines with new indications (for public health) should be given conditional registration subject to a plan that includes CEM.
- The final manual on CEM should be translated into French, Spanish and Portuguese.
- Malaria programme should strengthen support for CEM of new ACTs.
- Drug regulations should include CEM as well as spontaneous reporting as part of regular pharmacovigilance activities.

### Networking

Presentations were made on the various networks existing in Africa. A network was defined as an opportunity to expand contacts and create and nurture quality relationships. The existing pharmacovigilance networks include the Vigimed electronic exchange from the Uppsala Monitoring Centre (the UMC), the regulatory part of the Southern African Development Community (SADC), the pharmacovigilance part of the recently formed Eastern African Community (EAC), an informal francophone pharmacovigilance network and an emerging pharmacovigilance network between Ghana, Nigeria and Sierra Leone. There are also networks for vaccine programmes and malaria programmes and possibly also other public health programmes.

It was agreed that different networks serve different purposes but it was important to be aware of them.

Action points from the session on networking:

- A secure web-based community should be created for the pharmacovigilance consultants and expanded to include others as appropriate.
- Relevant networks in malaria, HIV/AIDS, TB and vaccines programmes should be identified and listed on the Community Homepage.
- The network should be moderated. A coordinator should be identified to maintain the network. Funds should be identified from WHO for this function.
- In the future, a developed network should not exclude any country.
- Language should not be a barrier to networking; must find technical and practical solutions.
- Annual National Centres meetings should serve as a platform for effective networking. WHO should provide financial support for participation at these meetings.

### Quality issues

Quality of medicines cannot be assessed, tested or inspected but has to be built into the manufacture of the products. It is the responsibility of the manufacturers to implement Good Manufacturing Practice (GMP). Quality requirements and control methods, proposed by the manufacturer and approved by regulatory authorities, are based on pre-defined criteria - e.g. pharmacopoeias. One of the main problems is that there is a paucity of prequalified laboratories. The prequalification scheme was created by the World Health Organization in 2001. It aims to increase access to priority medicinal products that meet unified standards of acceptable quality, safety and efficacy, currently focusing on those used for HIV/AIDS, Malaria, Tuberculosis and for Reproductive Health. The Programme undertakes comprehensive evaluation of the quality, safety and efficacy of medicinal products, based on information submitted by the manufacturers, and inspection of the corresponding manufacturing and clinical sites. The Programme also prequalifies quality control laboratories of pharmaceuticals.

### Database issues

A presentation was made on the methods of data processing. The UMC presented the options for electronic reporting of adverse drug reactions (ADRs) available to national pharmacovigilance centres. The UMC has developed a tool (Vigiflow) for electronic reporting of ADRs that is of reasonable cost and is simple to use. It is E2b compatible, has support for several languages, uses WHO-standard tools (WHO drug dictionary, WHO-DD; WHO adverse reaction terminology, WHO-ART). Each National Centre has its

data stored in Uppsala and these are accessed via the internet. The individual Centre's data are secure and cannot be accessed by any other party. An adaptation for data collection for cohort event monitoring will be developed.

The action points from the discussion were:

- Countries should consider Vigiflow as an appropriate tool for data management of ADR reports.
  - Broad search strategies should be used when retrieving data from the WHO global database (Vigibase), both in regard to ADR search terms and the use of the Anatomical, therapeutic, chemical (ATC) codes for related medicines.
- Use of WHO drug dictionary as a reference tool for drug names should be considered

WHO-ART should be the preferred terminology for recording ADRs. When needed, countries should use new terms for events not currently included in WHO-ART. These terms should then be included in the report forwarded to the UMC for their assessment and inclusion in WHO-ART.

### **Complex issues**

A session was held to discuss various complex issues that occur in the course of pharmacovigilance. The discussion provided the following action points:

- Local safety data should be collected; existing data should be shared with WHO and the UMC.
- A six-country study to provide evidence of the need for pharmacovigilance should be carried out and published as a health and economic justification for policy makers, politicians and other stakeholders.
- The broadening scope of pharmacovigilance should be reinforced to include counterfeit, substandard and quality defects. This is a high priority in Africa.
- The transparency of processes in evaluating and communicating the benefit / harm of medicines should be increased.
- Collaboration with the pharmaceutical industry at country level with emphasis on patient safety should be improved.
- The involvement of patients/consumers should be sought to improve medicine safety.
- Complex medicine safety problems should be resolved through regional and international collaboration.

### **Root cause analysis**

This was presented to the consultants as an important method to identify causes of medication related problems: Root cause analysis and fault tree analysis are systematic investigation techniques looking beyond the affected individuals and seeking to understand the underlying causes and environmental context in which the incident happened. The analyses focus on identifying the hidden conditions that underlie variations in performance and on developing recommendations for improvements to decrease the likelihood of a recurrence. They comprise design, implementation, evaluation and the follow-up of improved safety systems. Techniques are usually applied to serious adverse events or critical incidents also known as sentinel events.

- A WHO pilot project is currently under way to explore a method for identifying causes of medication error to improve patient safety. Results from this pilot project are awaited before any definite recommendations on the use of these techniques can be made.

### **Drug Utilization Studies**

The group discussed the importance of defined daily dose (DDD) and prescribed daily dose (PDD). DDD of medicines allow calculation of drug consumption in communities. In particular these units are useful in comparing international use of medicines. PDD on the other hand help understand clinical and prescribing practices. There are other objective measures or indicators that help describe / define drug use in a community:

1. Prescribing indicators include average number of drugs prescribed per encounter, number of antibiotics prescribed, number of injections prescribed, adherence to Essential Medicines Lists (EML).
2. Patient care indicators include average consultation time with patient, dispensing time, percentage of drugs adequately labelled.
3. Facility indicators include availability of EML in the facility, availability of key drugs in the facility.

The above three are 'Core drug use indicators'.

'Supplementary indicators' may be needed to further substantiate data from core drug use indicators. Measuring the core drug use indicators is only the first step towards focusing attention on a particular problem, e.g. inappropriate/excessive use of injections in children in a health facility in Indonesia. A focused group discussion might however be needed to understand the reasons underlying the observed problem. Appropriate interventions would then depend on the results of such a focused discussion.

Recommendations from group discussion on above:

- Presence of a functional pharmacovigilance centre might be added as a facility indicator. The general principles of developing and employing drug use indicators could be useful in developing tools or criteria for evaluating a pharmacovigilance centre.

### Overcoming barriers

The Consultants discussed barriers are those factors that discourage people from taking an action they would otherwise do. If any health action is to be widely adopted, common barriers to doing the action must first be removed. Social marketing exchange theory advises that desired actions can be made more attractive by minimizing key barriers. This is also true for pharmacovigilance. Before designing a country PV programme there is a need to:

- identify the specific barriers;
- see how others have addressed these barriers;
- delete those solutions that are not practical for the country in question;
- add other solutions that might work well in this specific case.

In the list of barriers, consider each barrier, indicate a low, medium or high investment requirement and weigh the importance of each barrier, expected benefit from overcoming it, against the expected investment. Economic difficulties, infrastructure gaps, lack of communication are some of the well known barriers to any kind of development project. But quite often the mind set and individual biases are frequent barriers to implementing a project. Individual, real-life examples and field experiences in health-care settings, both as a patient and as a care-giver, need to be drawn upon and shared to inspire interest in pharmacovigilance.

### Next Steps

- A Follow-up meeting should be convened in one year; the action points as identified in this report are to be pursued by the consultants and results reported at this time.
- Briefing notes are to be prepared by WHO and sent to the World Health Organization Representatives (WRs) in Africa by end of August; the briefing notes prepared by the consultants should be distributed as widely as possible.
- An E-Network for the consultants should be activated on WHO's Health Technology and Pharmaceuticals technical knowledge portal, MEDNet (<http://mednet.who.int>) by 15 July 2007.
- The manual on Expecting the Worst (see under publications at [www.who-umc.org](http://www.who-umc.org)) should be adapted for developing a Standard Operating Procedure (SOP) for medicinal crisis management.

A text book on pharmacovigilance in Africa should be published and guidelines for effective communication developed by WHO.

The meeting was officially closed by the WR in Ghana and appreciation was expressed to the University of Ghana Medical School, Accra, Ghana who were the prime organizers of the meeting.