In this issue we bring you the recommendations from the fifth meeting of the Advisory Committee on Safety of Medicinal Products (ACSoMP). Some of the recommendations relate to ongoing projects, such as the patient safety pilot project for expanding the scope of national pharmacovigilance centres; others refer to new initiatives, such as developing indicators for measuring pharmacovigilance capacity and the impact of interventions in countries. Worldwide serious, acute allergic-type reactions have been reported in patients who received contaminated heparin. We have included a brief summary of regulatory actions that followed these events.
## Regulatory Matters

- Chlorproguanil/ dapsone/artesunate
- Deferasirox
- Injectable colchicine
- Ketoconazole
- Meprobamate
- Modafinil
- Mycophenolate mofetil and mycophenolic acid
- Oseltamivir
- Telbivudine
- Zanamivir
- Zolpidem

## Safety of Medicines

- Abacavir, didanosine
- Antiepileptics
- Becaplermin
- Botulinum toxins
- Darunavir
- Exubera short acting insuling 'breathe-in' preparation
- Fentanyl transdermal patches
- Montelukast
- Natalizumab
- Nicorandil
- Tiotropium
- Topiramate

A Short report on recent events related to the acute allergic-type reactions reported with the use of heparin in some haemodialysis patients

Advisory Committee on Safety of Medicinal Products (ACSoMP), 25 - 27 February 2008, WHO Headquarters, Geneva
Chlorproguanil/dapsone/artesunate

Further development of 'triple' combination product terminated; 'double' combination product recalled

Worldwide. GlaxoSmithKline (GSK) and Medicines for Malaria Venture (MMV) have decided to terminate the further development of Dacart™, a fixed-dose combination antimalarial product of chlorproguanil, dapsone and artesunate (CDA). GSK has also commenced a product recall process at pharmacy level in Kenya, for LapDap™, another anti-malarial product containing chlorproguanil and dapsone (CD). These decisions are based on data from two Phase III clinical trials assessing the efficacy and safety of CDA (Dacart™) and CD (LapDap™); significant reductions of haemoglobin levels in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency have been observed with both CDA and CD. Chlorproguanil-dapsone (LapDap™) was granted a marketing authorization in July 2003 by the United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA) for the treatment of uncomplicated falciparum malaria. Chlorproguanil-dapsone (CD) was contraindicated in patients with known G6PD deficiency. In view of the potential widespread use of CD (LapDap™) in malaria endemic sub-Saharan Africa, the high prevalence of G6PD deficiency in the region (estimated to affect around 10-25% of the population in sub-Saharan Africa) and the limited availability of screening tests for this genetic condition in Africa, WHO had undertaken a safety assessment of the product in 2004, to provide recommendations on the safe use of CD (LapDap™) in Africa. The WHO expert group cautioned against the use of the medicine in G6PD deficient patients and made the following recommendations:

1. This medicine should be used only if a diagnosis of malaria is confirmed.
2. CD should be used only after severe anaemia (haemoglobin concentration < 5 g/dl) and G6PD deficiency have been excluded by appropriate tests. In patients with a haemoglobin concentration of 7 g/dl, administration of CD should be considered with caution and should be undertaken only under clinical supervision, with monitoring of the haemoglobin concentration. The diagnosis of methaemoglobinemia is less important.
3. In areas where G6PD deficiency is prevalent but appropriate tests are not available, an alternative antimalarial medicine should be used.
4. If there is no suitable alternative, CD should be used but in cognizance of the haematological risks associated with this medicine. The group also advised that these recommendations should be reevaluated when more data becomes available from pharmacovigilance and active post-marketing surveillance.

The WHO safety assessment report also provided a series of recommendations for ongoing and planned clinical trials as well as phase IV studies to gather the necessary evidence on safety of CD (LapDap™), including in malaria patients with G6PD deficiency. However, several CD (LapDap™) phase IV studies which started in African countries did not continue beyond April 2006 due to low utilization of this medicine. Research on the safety aspects mainly continued as part of the Medicines for Malaria Venture (MMV) - sponsored studies on chlorproguanil-dapsone-artesunate (CDA).

GSK’s multi-center, double-blind Phase III clinical trial of chlorproguanil-dapsone-artesunate (CDA) versus the combination antimalarial lumefantrine-artemether (Coartem®) in Africa suggest a strong association between haemolytic anaemia and CDA treatment for uncomplicated falciparum malaria in G6PD deficient patients. The study included 1372 patients. Study results showed a significant reduction in haemoglobin due to haemolytic anaemia in patients with G6PD deficiency, with lowest levels of haemoglobin occurring seven days after treatment. At day seven, 35% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 2g/dl compared to 8% of patients treated with Coartem®, and 10% of the patients with G6PD deficiency treated with CDA had a reduction in haemoglobin of more than 4g/dl compared to 0% of patients treated with Coartem®. 38% of the male patients with G6PD deficiency had severe anaemia after treatment with CDA, compared to 0% in the group treated with Coartem®. In total, 15 patients had severe post-treatment haemolysis requiring blood transfusion in the study: all 15 were in the CDA treated group, 13 of whom were G6PD deficient.

References:
Deferasirox
Reports of hepatic failure

Canada, USA. Novartis has issued a public communication and a 'Dear Health-care Professional' letter, advising of updated safety information regarding reports of hepatic failure with deferasirox (Exjade). According to Novartis, cases of hepatic failure have been reported internationally following post-marketing use of deferasirox; some of the cases had a fatal outcome. Most of the cases involved patients with multiple medical conditions, including multi-organ failure and liver disease (cirrhosis). The deferasirox (Exjade) product monograph has been updated accordingly (although a causal relationship between deferasirox and hepatic failure has not been established). There have been a total of 24 international reports of hepatic failure (21 from postmarketing, three from clinical trials); the estimated total cumulative exposure to deferasirox (Exjade) was 36,797 patients as of 31 October 2007. No patient with normal liver function or without additional life-threatening complications has developed liver failure. The company reminds health-care professionals that liver function should be monitored monthly and that deferasirox should be discontinued if there is unexplained, persistent and progressive liver function deterioration. Novartis says that a post-marketing report of hepatic failure and encephalopathy was reported to the United States Food and Drug Administration (US FDA) by a patient in the US. The patient, who had a history of alcohol use and slightly abnormal liver function, received deferasirox for five days. The patient received deferasirox for a non-approved use while having a serum ferritin level of >10 times lower than the recommended level for deferasirox initiation. Following discontinuation of deferasirox, the patient recovered. Although the potential role of deferasirox in this case could not be excluded, following a review, Novartis and external medical experts agreed that there were extenuating circumstances in this case.

(Novartis Pharma had also issued a letter about possible association between the use of deferasirox and renal failure and cytopenia that were reported in Canada and in Switzerland; see WHO Pharmaceuticals Newsletter No. 2, 2007.)

Reference:

Injectable colchicine
Action against unapproved injectable colchicine

USA. The US FDA intends to take regulatory action against companies marketing unapproved injectable colchicine, a drug used to treat gout. The Agency emphasizes that colchicine is highly toxic and can easily be given in excessive doses, especially when administered intravenously. The US FDA is aware of 50 reports of adverse events associated with intravenous colchicine use, including 23 deaths. It says that three of the deaths, which occurred in March and April 2007, were associated with the use of compounded colchicine that was eight times more potent than stated on the label, due to a preparation error. The US FDA explains that, in addition to being manufactured by pharmaceutical companies, injectable colchicine products are sometimes manufactured by compounding pharmacies, often for the treatment of back pain. The Agency notes that it has not approved colchicine in any dosage form for the treatment of back pain.

Reports in the WHO ICSR database:
Colchicine - injectable
Death - 14

Reference:

Ketoconazole
Several indications removed

UK. The prescribing information for ketoconazole (Nizoral) tablets has been updated with the removal of several therapeutic indications because of the risk of serious hepatotoxicity and unavailability of other effective antifungals. Following a review of risks and benefits, the MHRA advises that oral ketoconazole should only be used for malassezia folliculitis, dermatophytosis and chronic candidosis, which cannot be treated topically. Ketoconazole should only be used in patients with infections resistant to fluconazole, terbinafine or itraconazole, or in patients who are intolerant to these drugs. The agency notes that the risk of serious hepatotoxicity increases with duration of oral ketoconazole treatment and that courses of >10 days should only be given after balancing risks and benefits of continued treatment and full consideration of the extent of treatment response. The MHRA advises health-care professionals that liver function must be monitored prior to ketoconazole initiation, at week two and four of therapy, and continued monthly. If any liver function parameters are higher than three times the
normal limit, ketoconazole should be discontinued.


Meprobamate
Benefit/risk profile no longer favourable

UK. The MHRA no longer considers the balance of benefits and risks for meprobamate-containing products to be favourable. Meprobamate is a carbamate used for short-term treatment of anxiety states or musculoskeletal disorders with muscle tyension or painful muscle spasm. The Agency advises that there are risks of dependence, withdrawal, abuse and other unpleasant adverse effects associated with meprobamate; that there are safer alternatives to meprobamate. The MHRA is in discussion with the three UK marketing authorization holders for meprobamate products about a phased withdrawal of these products from the UK market. The Agency is advising health-care professionals that treatment with meprobamate should not be initiated. (Meprobamate is the main active metabolite of carisoprodol; the EMEA has recommended suspending the marketing authorization for all medicinal products containing carisoprodol because the risks from these medicines outweigh their benefits; see WHO Pharmaceuticals Newsletter No. 6, 2007).


Modafinil
Risk of psychiatric symptoms; serious skin reactions

UK. The MHRA has advised that modafinil (Provigil) product information has been updated to include the risk of psychiatric symptoms and serious skin reactions. Modafinil is a drug used to treat excessive sleepiness caused by narcolepsy. Stevens Johnson syndrome, toxic epidermal necrolysis and erythema multiforme have been reported in association with modafinil. These reactions have usually occurred within five weeks of treatment, but isolated cases have occurred after > 3 months. Hallucinations, delusion, aggression, suicidal ideation, psychosis and mania have also been reported in association with modafinil. These conditions have mainly occurred in patients with a history of mania, depression or psychosis. The MHRA advises health-care professionals that modafinil should be permanently discontinued at the first sign of rash or psychiatric symptoms. The agency also advises that modafinil should be used with caution in patients with a history of depression, mania, psychosis, or alcohol, drug or illicit substance abuse. (See WHO Pharmaceuticals Newsletter No. 1, 2008 for serious skin reactions reported with modafinil in Canada).

Reports in WHO ICSR database:
Modafinil – 1997 - 2008

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Mycophenolate mofetil and mycophenolic acid
Reports of multifocal leukoencephalopathy

Europe, USA. Mycophenolate mofetil (CellCept) is approved to prevent heart, liver, and kidney transplant rejection and mycophenolic acid (Myfortic) is approved to prevent kidney transplant rejection. Mycophenolate mofetil is metabolized in the body to mycophenolic acid. Both these products are used with other drugs to suppress the immune system. On February 2008 Roche wrote to health-care professionals in Europe about isolated cases of progressive multifocal leukoencephalopathy (PML) that were observed in patients receiving mycophenolate mofetil (CellCept). Roche wrote that although confounding factors, in particular the underlying disease were associated with these cases of PML, the contributory role of mycophenolate mofetil could not be excluded. The Summary of Product Characteristics (SPC) for mycophenolate mofetil has been updated to reflect this information. Later, on March 2008, Roche informed the US FDA about this letter that was issued in Europe. US FDA is reviewing all relevant data, and has also asked Novartis, the maker of mycophenolic acid (Myfortic), for data on PML cases and to revise the mycophenolic acid prescribing information to include the same information about PML as included in the mycophenolate mofetil prescribing information. When completed, the Agency will communicate the conclusions of its review to the public. PML is a rare disorder that affects the central nervous system. It usually occurs in patients with immune systems suppressed by disease or medicines. Signs and symptoms of PML can include localized neurologic signs and symptoms.
including vision changes, loss of coordination, clumsiness, memory loss, difficulty speaking or understanding what others say, and weakness in the legs. Many patients who develop PML die and those who survive may have permanent disability due to irreversible nerve damage.

References:
2. Communication about an ongoing safety review of CellCept (mycophenolate mofetil) and Myfortic (mycophenolate acid). US FDA, 10 April 2008 (www.fda.gov).

Oseltamivir
Label to include information on neuropsychiatric events

USA. The oseltamivir(Tamiflu) prescribing information has been updated to reflect the US FDA Pediatric Advisory committee recommendations regarding neuropsychiatric events. The label will now include information regarding an association between influenza and neuropsychiatric adverse events and that these reports are uncommon. The label has been revised as follows: Influenza can be associated with a variety of neurologic and behavioral symptoms which can include events such as hallucinations, delirium, and abnormal behavior, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. There have been postmarketing reports (mostly from Japan) of delirium and abnormal behavior leading to injury in patients with influenza who were receiving oseltamivir (Tamiflu). Because these events were reported voluntarily during clinical practice, estimates of frequency cannot be made but they appear to be uncommon based on oseltamivir (Tamiflu) usage data. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of oseltamivir (Tamiflu) to these events has not been established. Patients with influenza should be closely monitored for signs of abnormal behavior. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

(Please refer to WHO Pharmaceuticals Newsletter No. 6, 2006 and No. 2, 2007 for previous postings on oseltamivir and neuropsychiatric events.)

WHO adverse reactions database:
Oseltamivir (Tamiflu) - reported 2000 – 2008
Totally 140 reports; main reactions:
- Anxiety: 11
- Nervousness: 13
- Anorexia: 23
- Hallucination: 23
- Insomnia: 34
- Agitation: 14
- Confusion: 26

Reference:
'Dear Health-care Professional' letter from Roche, February 2008 (www.fda.gov).

Telbivudine
Risk of peripheral neuropathy

Europe: The European Medicines Agency (EMEA) has recommended adding new warnings about the risk of peripheral neuropathy in the product information for telbivudine (Sebivo). An increased risk of peripheral neuropathy was observed in a clinical trial investigating combined therapy with telbivudine 600mg daily and peginterferon-α-2a 180µg once weekly. Peripheral neuropathy has been uncommonly reported in patients receiving telbivudine monotherapy. The product information for telbivudine will now include warnings of an increased risk of peripheral neuropathy when telbivudine and peginterferon-α-2a are co-administered. An increased risk cannot be excluded for other interferons-α (pegylated or standard). The EMEA has advised that if peripheral neuropathy is suspected, telbivudine treatment should be reconsidered. Benefits of concomitant therapy with telbivudine and interferon-α have not been established.

Reference:

Zanamivir
Reports of delirium and abnormal behaviour

USA. The WARNINGS AND PRECAUTIONS sections of the prescribing information for zanamivir (Relenza) has been updated with information from postmarketing reports (mostly from Japan) of delirium and abnormal behaviour leading to injury in patients with influenza who were receiving neuraminidase inhibitors, including zanamivir. These events were reported primarily among pediatric patients and often had an abrupt onset and rapid resolution. The contribution of zanamivir to these events has not been established. Influenza can be associated with a variety of neurologic and behavioural symptoms which can include seizures, hallucinations, delirium, and abnormal behaviour, in some cases resulting in fatal outcomes. These events may occur in the setting of encephalitis or encephalopathy but can occur without obvious severe disease. Health professionals are
advised to monitor patients for signs of abnormal behaviour. If neuropsychiatric symptoms occur, the risks and benefits of continuing treatment should be evaluated for each patient.

Reference:
'Dear Health-care Professional' letter from GlaxoSmithKline, 11 March 2008 (www.fda.gov).

Zolpidem
Boxed warning added about sleep disorders

Australia. The Australian Therapeutic Goods Administration (TGA) has introduced a boxed warning for medicines containing zolpidem. This decision is based on reports of bizarre and sometimes dangerous sleep disorders in patients who have received the drug (see WHO Pharmaceuticals Newsletter No. 2, 2007). The TGA notes that up until 4 January 2008, its adverse reactions database contained 1032 reports of suspected adverse drug reactions to zolpidem products, 394 of which mentioned abnormal sleep-related events such as sleep walking, sleep eating and sleep driving. The boxed warning states that zolpidem may be associated with potentially dangerous complex sleep-related behaviours such as sleep walking, sleep driving and other bizarre behaviours. Furthermore, the warning stipulates that zolpidem should not be taken with alcohol, that caution is necessary with other CNS depressants, and that use of zolpidem should be limited to a maximum of four weeks under close medical supervision.

Reports in the WHO ICSR database:
Dreaming abnormal 51
Paroniria 143
Somnambulism 123

Reference:
Abacavir, didanosine

Increased risk of heart attack

USA, Europe. The Data Collection on Adverse Events of Anti-HIV Drugs study or the D:A:D study was initiated in 1999 as a prospective observational study to determine associations between the use of anti-HIV medicines and the risk of cardiovascular disease in HIV patients in Europe, Australia and the United States. The study includes more than 33,000 patients so far. Data from the study suggest an increased risk of heart attack (myocardial infarction, MI) associated with the use of abacavir-containing medicines. Abacavir is a nucleoside reverse transcriptase inhibitor (NRTI). A similar but weaker association was seen with didanosine, another NRTI. However, the EMEA and the US FDA are of the opinion that further analyses are needed to determine the risk of MI with these medicines. The Agencies will continue to evaluate the overall risks and benefits with these drugs and will share additional information when available. In the meantime health-care professionals are advised to evaluate the potential risks and benefits of these medicines for their HIV patients.

Reference:

Antiepileptics

Risk of suicidal ideation almost double with antiepileptics

USA. A US FDA analysis of 199 placebo-controlled clinical studies involving 11 different antiepileptic drugs revealed that the risk of suicidal ideation or behaviour is almost double in patients receiving antiepileptic drugs than in those receiving placebo. The analysis included 43,892 patients (aged ≥ 5 years) who were randomized to receive antiepileptic drugs (n = 27,863) or placebo; the conditions studied in the trials included epilepsy, psychiatric disorders like anxiety, depression and bipolar disorder, and other conditions like neuropathic pain syndromes and migraine. Four completed suicides were observed in the antiepileptic drug group and none in the placebo group. Risk of suicidal ideation and suicidal behaviour was significantly higher in the antiepileptic group than in the placebo group. Overall, 0.43% of the antiepileptic recipients and 0.22% of the placebo recipients experienced suicidal ideation or behaviour; an estimated 2.1 per 1000 more patients in the antiepileptic drug group experienced suicidal ideation or behaviour than in the placebo group. The increase in risk was observed as early as one week after drug initiation and continued to at least 24 weeks. The relative risk for suicidal ideation or behaviour was higher for patients with epilepsy than in those with psychiatric or other disorders. Following the results of the analysis by the US FDA, New Zealand’s regulatory Agency, Medsafe, has alerted health-care professionals about the increased risk of suicidal thoughts and behaviours in antiepileptic drug recipients. Medsafe has advised patients who are receiving antiepileptic drugs to consult their doctors before making any changes to their drug regimen.

*carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproic acid and zonisamide

References:

Becaplermin

May increase risk of death from cancer in diabetic patients

USA. The US FDA is conducting a safety review based on study data suggesting there may be an increased risk of death from cancer in diabetic patients using becaplermin gel (Regranex Gel), a skin product used to heal leg and foot ulcers. The study used health insurance plan database of patients with diabetes who were at least 19 years of age or older and who had no history of cancer; there were more deaths due to cancer from among the people who had been prescribed becaplermin gel three times or more. There was not enough information to conclude whether there was an increase in the number of patients that developed new cancers. The US FDA cautions that there are known risks associated with diabetic foot and leg ulcers that do not heal. The Agency recommends that, while the review is ongoing, health-care professionals should discuss the potential risks and benefits of using becaplermin gel with their patients. As soon as this review is complete, the US FDA will communicate the conclusions and recommendations to the public.

Reference:
Botulinum toxins

Reports of systemic adverse reactions

USA. The US FDA has issued an early communication about its ongoing review of safety data for botulinum toxin A (Botox and Botox Cosmetic) and botulinum toxin B (Myobloc). The Agency says that it has received reports of systemic adverse reactions including respiratory compromise and death, suggestive of botulism, associated with the use of these products. Most of the reported cases involved children who had received the drugs for cerebral palsy-associated limb spasticity, a condition these botulinum toxins are not approved to be used for in the US. According to the Agency, the efficacy, safety and dosage of botulinum toxins have not been established for the treatment of cerebral palsy-associated limb spasticity; the toxins are not approved for use in children aged < 12 years. Until the review is completed, the US FDA has advised health-care professionals of the following:

- To understand that clinical doses are not comparable from one botulinum product to the next.
- To be alert to the potential of systemic effects following administration of botulinum toxins A and B.
- To understand that systemic effects can develop as early as one day and as late as several weeks after treatment.
- To provide patients and caregivers with the information needed to identify the signs and symptoms of systemic effects.
- To advise patients to seek immediate medical attention if they develop worsening or unexpected difficulty swallowing or talking, muscle weakness or breathing trouble.

A review of the US FDA’s Adverse Event Reporting System (AERS) database and the medical literature revealed that pediatric botulism developed in patients aged < 16 years and serious outcomes included hospitalization and death. No deaths were reported among adult cases of botulism. In botulism cases, botulinum toxin A doses ranged from 6.25 to 32U/kg in children and from 10 to 700U in adults, whereas botulinum toxin B doses ranged from 388 to 625U/Kg in children and from 10 000 to 20 000U in adults.

WHO ICSR database:

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Reference:
Early communication about an ongoing safety review of Botox and Botox Cosmetic (botulinum toxin Type A) and Myobloc (botulinum toxin Type B). US FDA, 8 February 2008 (www.fda.gov).

Reference:

Darunavir
Reports of hepatitis

USA. Tibotec Therapeutics has updated the WARNINGS section of the prescribing information for darunavir (Prezista) tablets regarding the risk of hepatotoxicity. Darunavir is a protease inhibitor indicated for use with other antiretroviral agents in the treatment of HIV infection in adults. In clinical trials and postmarketing experience, drug induced hepatitis has been reported in patients receiving combination therapy with darunavir/ritonavir. Health professionals are cautioned that appropriate laboratory testing should be conducted prior to initiating therapy with darunavir/ritonavir and that patients should be monitored during treatment. Increased AST/ALT monitoring should be considered in patients with underlying chronic hepatitis, cirrhosis, or in patients who have pretreatment elevations of transaminases, especially during the first several months of darunavir/ritonavir treatment.

Exubera short acting insuling 'breathe-in' preparation

Six new cases of primary lung malignancies

USA. Pfizer has informed health-care professionals about six newly diagnosed cases of primary lung malignancies in clinical trials among patients treated with the short acting insulin preparation, Exubera. (Patients breathe-in the preparation, by mouth, using the Exubera inhaler). There has also been one post-marketing report of a primary lung malignancy in an Exubera-treated patient. Pfizer notes that at this point there are too few cases to determine whether the emergence of these events is related to the product (Exubera). All patients who were diagnosed with lung cancer had a prior history of cigarette smoking. Because of the limited availability of Exubera, health-care professionals are advised to seek alternative
treatment options to maintain patients’ glycemic control.

**Reference:**

**Fentanyl transdermal patches**

**Reminder about safe use**

**USA.** The US FDA has issued a second safety warning concerning fentanyl transdermal patches, prompted by continuing reports of death and life-threatening adverse events after either inappropriate prescribing or incorrect use by patients. The Public Health Advisory, similar to that first issued in July 2005 (see WHO Pharmaceuticals Newsletter No. 3, 2005) emphasizes that fentanyl patches are only for patients who are opioid-tolerant and have chronic pain that is not well controlled by other analogics. The transdermal opioid should not be used to manage sudden, occasional or mild pain, or short-term postoperative pain. Also, both prescribers and patients using fentanyl patches should be aware of the signs of fentanyl overdose. The Agency is also asking Johnson & Johnson, (manufacturer of the Duragesic fentanyl patch), and all manufacturers of generic fentanyl transdermal patches to update their product information and to develop a medication guide for patients.

- Death - 1367 (by transdermal or topical use).

**Reference:**  
Public Health Advisory.  

**Montelukast**

**Possible association with behaviour/mood changes, suicidality, suicide**

**USA.** US FDA is investigating a possible association between the use of montelukast (Singular) and behavior/mood changes, suicidality (suicidal thinking and behavior) and suicide. Montelukast is a leukotriene receptor antagonist used to treat asthma and the symptoms of allergic rhinitis (sneezing, stuffy nose, runny nose, itching of the nose) and to prevent exercise-induced asthma. Merck & Co, Inc., has updated the prescribing and patient information for montelukast with the following post-marketing adverse events:  
- tremor (March 2007),  
- depression (April 2007),  
- suicidality (suicidal thinking and behavior) (October 2007), and  
- anxiousness (February 2008).

The US FDA is working with Merck to further evaluate the possible association between these adverse events and montelukast. Montelukast is an effective medicine in the treatment of asthma and symptoms of allergic rhinitis; but health-care professionals and caregivers should monitor patients taking montelukast for signs of suicidality and changes in behavior and mood. The US FDA is also reviewing post-marketing reports of similar adverse events with other leukotriene modifying medications, e.g. zafirlukast, (another leukotriene receptor antagonist) and zileuton (a leukotriene synthesis inhibitor) to determine if additional investigations are needed. Conclusions and recommendations from the review will be communicated to the public when completed.

**Reference:**  
Early Communication about an Ongoing Safety Review of Montelukast (Singular).

**Natalizumab**

**Reports of liver injury**

**USA.** Natalizumab (Tysabri) was suspended (voluntary suspension by Biogen Idec) in 2005 following two cases of progressive multifocal leukoencephalopathy observed in patients enrolled in a clinical trial who had been receiving the drug for multiple sclerosis for more than two years (1). But later, in 2006, natalizumab was reintroduced in the US under a restricted use / risk management plan (2) as a monotherapy for patients with relapsing forms of multiple sclerosis. The manufacturers (Biogen Idec and Elan), in collaboration with the US FDA, have now, more recently, notified health-care professionals of reports of clinically significant liver injury, including markedly elevated serum hepatic enzymes and elevated total bilirubin, that occurred as early as six days after the first dose of natalizumab (3). The combination of transaminase elevations and elevated bilirubin without evidence of obstruction is recognized as an important predictor of severe liver injury that may lead to death or the need for a liver transplant in some patients. Health professionals are advised to discontinue natalizumab in patients with jaundice or with other evidence of significant liver injury and to inform their patients that natalizumab may cause liver injury.

**Reference:**  
1. WHO Pharmaceuticals Newsletter No. 4, 2006 (www.who.int).  
3. 'Dear health-care professional' letter from

WHO ICSR database: Natalizumab
Liver disorders 16 reports, all from USA:

- Hepatic failure 1
- Hepatic function abnormal 3
- Hepatitis viral 1
- Hepatic cirrhosis 1
- Hepatitis 1
- Hepatitis chronic active 1
- Hepatocellular damage 1
- Liver fatty 2
- Coma hepatic 2
- Hepatic enzymes increased 5
- Hepatomegaly 1
- Hepatorenal syndrome 1
- ALT/AST increased 3

Nicorandil
Reports of ulceration

Australia. Nicorandil (Ikorel) is a synthetic nicotine derivative indicated for the treatment of chronic stable angina pectoris at a dose of 10-20 mg daily. Seven of 51 reports received by the Australian Therapeutic Goods Administration (TGA) for nicorandil describe ulceration. Patients were 57-88 years old, and six were female. Where stated, the daily dose was 20mg (n=3) or 40mg (n=2) and the time to onset of ulceration after starting nicorandil ranged from one day to many months. Six of the seven reports described tongue or mouth ulcers. Nicorandil-associated ulceration has been reported in the oral mucosa, anal, perianal, vulvar, perivulvar, gastrointestinal and parastomal tissues, and various cutaneous sites, including the lower anterior leg, natal cleft, umbilicus and areas affected by flexural psoriasis; ulcers may occur at multiple sites. The reaction appears to be dose-related and the time to ulcer onset may be up to months after starting nicorandil. The ulcers are persistent, deep and ‘punched out’ in appearance, with non-specific inflammatory histology but resolve if the drug is withdrawn. In cases of recalcitrant ulceration, health professionals are advised to obtain patient’s drug history, and consider other inflammatory or neoplastic causes. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) warns that failure to recognize nicorandil-induced ulceration can lead to substantial morbidity, inappropriate investigation and treatment, and unnecessary surgery.

Reference:

Tiotropium
Increased risk of stroke

USA. Pulmonary care health professionals and patients are being warned that ongoing safety monitoring has identified a possible increased risk of stroke in patients who take tiotropium bromide (marketed as Spiriva HandiHaler). Tiotropium bromide is used to treat bronchospasm associated with chronic obstructive pulmonary disease. Boehringer Ingelheim reported to the US FDA that it has conducted an analysis of the safety data from 29 placebo controlled clinical studies (“pooled analysis”). Based on data from these studies, the preliminary estimates of the risk of stroke are eight patients per 1000 patients treated for one year with tiotropium, and six patients per 1000 patients treated for one year with placebo. This means that the estimated excess risk of any type of stroke due to tiotropium is two patients for each 1000 patients using tiotropium over a one year period. US FDA is working with Boehringer Ingelheim to further evaluate the potential association between tiotropium and stroke. In the mean time patients are advised to continue taking tiotropium bromide (Spiriva HandiHaler) and to talk to their doctor if they have questions about this new information.

Reference:

Topiramate
Reports of glaucoma

Australia. Topiramate is an antiepileptic indicated for either monotherapy or add-on therapy in adults and in children aged two years and over; and for the prophylaxis of migraine in adults. There are 11 reports of glaucoma in the 175 reports received so far with topiramate in Australia; nine involved females and two males with a median age of 36 (range, 22-47) years. Time to onset was within the first month of treatment in four reports, within the second month in two reports, and not stated in five reports. Five patients had recovered at the time of reporting, three had not yet recovered, and recovery status was unknown in the other three. ADRAC notes that a number of drugs have been associated with glaucoma; drugs most commonly reported to TGA include topiramate (11 reports), sertraline (10), tricapamide (7), venlafaxine (6) and ipratropium bromide (5). Because migraine itself may cause eye-pain, non-migraine causes should be considered in all patients treated with topiramate, who report eye pain. Topiramate should be stopped immediately in the event of topiramate-induced glaucoma and urgent medical treatment of the glaucoma should be initiated, failing which permanent vision loss can occur.

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Reference:
A Short report on recent events related to the acute allergic-type reactions reported with the use of heparin in some haemodialysis patients

One hundred and thirty one heparin-related deaths were reported to the US FDA between 1 Jan 2007 and 13 April 2008; these deaths occurred after heparin administration, regardless of cause. The US FDA notes that there has been an increase in events consistent with an anaphylactic-type reaction and/or acute hypotension. Of the 131 deaths, 81 were due to allergic symptoms (1).

On 17 January 2008, Baxter Healthcare Corporation began a voluntary recall of several lots of heparin sodium in the US after acute allergic-type reactions were reported in several haemodialysis patients who had received heparin manufactured by Baxter. The US FDA and Baxter have been conducting an investigation into these recent clusters of adverse reactions reported with heparin. The US FDA has detected a contaminant in Heparin active pharmaceutical ingredient (API) and crude heparin sourced from Changzhou SPL, Changzhou, China, as well as in the API from Scientific Protein Labs, Waunakee, Wisconsin U.S (2). In the US, this API was used in finished product distributed by Baxter Healthcare.

The US FDA has determined that the contaminated heparin batches contained 5-20% by weight of a contaminant that is a "heparin-like compound which is not heparin". The contaminant has been identified as an over-sulfated chondroitin sulfate (3). The US FDA has published two screening methods which can identify the presence of the heparin-like contaminant, the over-sulfated chondroitin sulfate; one of them involves proton nuclear magnetic resonance (NMR) spectroscopy, and the other involves capillary electrophoresis (CE). These tests are now mandatory for batch release of all heparin API preparations in the US (4).

In Germany, 80 or more recent cases of similar adverse events (no deaths) relating to specific batches of heparin products manufactured by Rotexmedica GmbH have also been reported. Rotexmedica initiated a recall on several batches of heparin injection in early March 2008 (5). The origin of the heparin in these products is the Changzhou Quianhong Bio Pharma Co. Ltd., China, and the Yantai Dongcheng Biochemicals Co., China.

Further recalls of heparin products from other suppliers have followed more recently, in the USA and elsewhere.

Heparin is on the WHO list of essential drugs, and WHO distributes the 5th International Standard Heparin for measurement of the potency of unfractionated heparin preparations according to methods outlined in the International Pharmacopoeia. Other WHO International Standards for heparin are the low molecular weight heparin standards for both biological activity and for molecular weight calibration. All the WHO International Standards for heparin have been found to be free of contamination according to criteria defined in the most recent version of the US FDA’s "Impurity evaluation of Heparin Sodium by NMR Spectroscopy" (6).

WHO can offer advice and help to National Regulatory Authorities in countries with limited resources for the characterization of suspect batches of heparin API, including testing by NMR and CE as recommended by the US FDA, through the WHO Collaborating Centre for Biological Standards and Control, Potters Bar, UK (7).

The WHO Expert Committee on Specifications for Pharmaceutical Preparations, which oversees the activities related to The International Pharmacopoeia, and the WHO Expert Committee on Biological Standardization will review the information about contaminants and impurities for heparin; this review will help decide if the existing quality control tests need to be revised in any way.

Adverse reactions to heparin products should be reported to the appropriate National Regulatory Authority. In general, for effective drug safety monitoring and global analysis, all national reports of adverse drug reactions and adverse events should be forwarded to the WHO Individual Case Safety Reports (ICSR) database, Vigibase, managed and maintained by the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden (8).

References:
2. Contaminant detected in heparin material of specified origin in the USA and in Germany; serious adverse events reported; recall measures initiated. Information Exchange System Alert No. 118, WHO, 7 March 2008 (www.who.int/medicines).
7. http://www.nibsc.ac.uk/
Summary of Recommendations
The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its fifth meeting in February 2008. Constituted to provide advice on pharmacovigilance (PV) policy, and issues related to the safety and effectiveness of medicinal products, the following is a summary of the Committee's recommendations:

Current and future trends of consumer reporting: how can WHO prepare itself or maximize this utility?
This session examined the lessons and perspectives learned from the United States of America (USA) and the European Union (EU), to see how WHO could prepare itself and develop a strategy to manage consumer reporting.

The experience of the US FDA which has always accepted consumer reporting of adverse events was presented. The underlying principle here is that a single responsible agency (US FDA) should deal with reports from consumers and that these reports receive equal weight during initial evaluation, regardless of source. The value of consumer reporting is that they are an important source of information that US FDA may not have otherwise received. They often contain relevant medical detail (although in lay terms). When needed, US FDA follows up with heath professionals for additional information on key cases. SSRIs and suicide and non-prescription products such as naproxen and oesophageal injury were cited as examples of medicines for which consumer reports had provided important additional information.

Current EU legislation does not include provisions for adverse event (AE) reporting by patients, but, since December 2007, the EU commission has a new legislative proposal for strengthening pharmacovigilance allowing patients to report AEs. Some Member States in the European Union (EU) have taken the initiative in favour of patient reporting - Denmark, France, Netherlands, Sweden, UK. The quality of patient reports was noted to be often very good. The percentage of serious reports appear to be comparable with health-care professional reports. A pilot study in Sweden during 2005-2007 was presented; there appears to be some indication that consumer reports may be an additional source of information on adverse drug reactions (ADRs), in particular AEs due to misuse of over-the-counter (OTC) drugs, and problems due to inadequate information in product leaflets.

Recommendations/action points:
It was emphasized that caution must be exercised with consumer reporting and that it should neither remove nor replace reporting by health-care professionals.

WHO will consider the elements that need to be in a consumer reporting form allowing some flexibility to permit consumers to narrate their story as this is helpful in making assessments. Countries with consumer reporting should send their reports to the WHO Collaborating Centre in Sweden, the Uppsala monitoring Centre (UMC).

A small working group will focus on this project development and the value of using data from consumer reporting; the ethics of managing the data should be developed into a guidance document. Consumer AE reporting project should liaise with the patient safety pilot project.

Developing a set of impact indicators specific to pharmacovigilance
This session dealt with a proposal for specific objective measures that will address the state of pharmacovigilance (PV) activities at three levels: characterizing PV in a country, the measures that assess the impact of PV interventions, and supervisory tools in detecting problems in implementation of those interventions. There is a need for a practical set of indicators for PV centres that will allow inter-country comparisons and will serve as a tool to leverage resource allocation for improvement.

Recommendations/action points:
ACSoMP is requested to define principles around developing a set of core and complementary indicators and to guide a process for arriving at a useful PV evaluation instrument. EU Framework may be a useful benchmark. A working group to develop this project further needs to be convened with the objective of finalizing the tool by the end of 2008.

Patient safety pilot project
The one-year patient safety pilot project has identified patient safety as an integral and existing part of the work of national pharmacovigilance centres. Vigibase, the WHO Individual Case Safety Reports (ICSR) database already contains much useful information on medication errors. An analysis of this data identified...
that interactions were especially important for medication errors and incidents were identified where medicines causing serious allergy had been re-administered. The pilot has also identified many functions that may be carried out by national PV centres: analysing their own databases for potential preventable medication errors, providing training in root cause analysis and educational seminars.

**Recommendations/action points:**
The committee recognizes the need to strengthen pharmacovigilance systems to detect, analyse, manage and prevent medication errors. Guidelines and training are recommended. Reporting of medication errors should be made as objective as possible. Consultations with World Alliance on Patient Safety on definitions and terminologies should be initiated.

**Cohort event monitoring (CEM) studies**
This session discussed CEM in Africa to collect data on medicines used in malaria. Cohort studies are based on observations in normal clinical practice when using available approved drugs in the market. Based on a training course held in Ghana two protocols have been submitted from Nigeria and the United Republic of Tanzania.

**Recommendations:**
Because sources of drug supplies and their quality have great variance, product identifiers (lot nos.) should be included in these study protocols. Lessons from practical problems encountered in CEM will be evaluated in these two pilot countries.

**The Chinese challenge: project to incorporate Chinese data**
A lot of quality ADR data is available in the national Chinese ADR database but stored in Chinese characters. The challenge the UMC is faced with is to make these case reports accessible in the global database for signalling purposes. A related challenge is to represent Chinese drug names in the WHO Drug Dictionary. If incorporated, these would benefit the research based pharmaceutical industry carrying out clinical trials in China. A WHO official letter has been sent to the Chinese State Food and Drug Administration (SFDA) calling for collaboration in the adaptation of Chinese ADR reports to the international standard format. The multinational pharmaceutical industry in China has also approached the UMC for a solution on compatibility of data. It is anticipated that these arrangements may take some time to be fully resolved. The current challenge in China includes time-consuming technical translation work and resolutions on resource mobilization and sharing. It is anticipated that resources may be generated collectively from health insurance agencies as well as drug industry associations.

**Leishmaniasis**
Visceral Leishmaniasis (VL) is a major public health problem in Bangladesh, India and Nepal. A description of a Leishmaniasis elimination project in these countries was presented. Until recently the antimonials and amphotericin B were the sole medicines available for the treatment of the disease. Oral miltefosine has now been found to be effective in hospital-based studies for the treatment of VL. However, a major concern with the medicine miltefosine is that it has been shown to be teratogenic in animal studies. It is contraindicated in pregnant women.

A project proposal has been initiated to identify the research needs to define the gaps and to generate appropriate tools that will help the disease control programmes to introduce pharmacovigilance for these medicines in their programmes. The Committee was informed of the progress that had been made in this area. Currently the full risk benefit profile of miltefosine is unknown. A risk management and minimization plan is being developed for the preventable adverse events.

**Recommendation/action points:**
Two committee members will assist in reviewing the Risk Management Planning framework of this project.

**Parasitic disease: ensuring safer use of drugs in preventive chemotherapy public health campaigns**
In both lymphatic filariasis (LF) and Schistosomiasis, mass treatment is undertaken with the help of non-health professionals (e.g. community volunteers and school teachers) without the benefit of a proper diagnosis. These programme managers need some guidance to detect drug reactions, report, manage and refer cases to a higher level. Safety of mass drug administration in loaisis and LF co-endemic areas was raised. Oversight committees to monitor serious ADRs are planned to better handle public health programmes including responding to crisis situation. These programmes asked ACSoMP for guidance and advice.

**Recommendations/action points:**
The publication 'Safety of Medicines in Public Health Programmes: pharmacovigilance an essential tool' should be used as the starting point for any guidance to the public health programmes. Mass drug administration programme managers are encouraged to communicate with their in-country national PV centres (where available) for assistance.

**Updates on HIV/AIDS programme: introducing PV in public health programmes**

While PV for antiretroviral (ARV) medicines in public health has achievements, PV needs to be integrated in the training and daily work of service providers. Moreover, there is need to harmonize terms and definitions, reporting and analysis of AEs linked to ARVs, and addressing gaps to transfer PV knowledge from industrialized/middle income countries to low income settings. The ARV/PV project aims to establish a process to develop regional and country capacity to manage and report AEs linked to ARV, and to stimulate collection of spontaneous reports by PV centres and promote active surveillance. This is an area where the HIV programme is asking ACSoMP for advice. The ACSoMP publication on ARV PV served as a good basis for developing the HIV/AIDs proposal.

**Recommendations:**
The UMC is to be asked to study how to manage ARV/AE data, including the use of definitions.

**Vaccines collaboration updates**

There is a need for improving the tools and services for the identification of vaccine related safety signals. This can be addressed by the appointment of a proposed officer for vaccine signal detection. The evaluation of signal detection is an ongoing process. Global network for safety surveillance for pandemic drugs and vaccines was discussed because during pandemics, there may be many other concomitant drug use that potentially interact with vaccines. There is a plan to establish a network of sentinel sites to monitor newly pre-qualified vaccines in the post marketing phase. The objectives are to ensure standardized approaches to monitor serious AEs, identify and address potential safety signals in a timely manner, and to ensure that the safety information is adequate to support immunization policy.

**Recommendation/action points:**
The 'Adverse Events Following Immunization (AEFI)' subgroup and the 'safety of vaccine formulation' subgroup of the Global Advisory Committee on Vaccine Safety (GACVS) will be working with the UMC for the improvement of AEFI detection and reporting, increasing the pool of vaccine signal reviews, and establishing methodologies for evaluating vaccine signals and evaluating excipients of vaccines causing AEFI.

**Preparedness for pandemic 'flu**

WHO is providing guidelines on regulatory preparedness for human pandemic influenza vaccines and generic operational guidelines. Because of many unknown facts, there is a need for safety assessments in practice that take into account time and work load constraints, role of different stakeholders and coordination. The activities at the national level will strengthen existing post-marketing surveillance systems.

**Recommendations:**
The Committee recommended that there should be a session at the thirty-first annual meeting of national PV centres.

**Hot topics of current interest**

**Human papilloma virus (HPV) vaccine**

A brief description on cervical cancer and HPV infection was presented. The link between HPV and cervical cancer provides the basis for vaccine development. There have been some reports of fatalities with the vaccine. Media attention of the fatal cases has confounded perception of the safety of the HPV vaccine (Gardasil). There was no identified pattern in the causes of death or in the time of these deaths. In six cases, causes of death were reported as pulmonary embolism, myocarditis, sepsis, meningitis. In three of these six cases, another vaccine was concomitantly given. In summary, the association between death and vaccination could not be assessed. 35 cases of Guillain Barré Syndrome (GBS) including Miller-Fisher variant were reported. Some were hearsay and were unconfirmed. The observed cases have confounding factors such as co-administration of Menactra. This issue is under further observation and assessment.

**Discussion:**
When this new vaccine is used more widely, there will be new unexpected adverse events. Good exposure data in real time is needed but this is an anticipated challenge. Background medical conditions of the subset of women population that will receive these vaccines should be known beforehand, in order to
assess attributable risk from vaccine exposure. This is also a current interest of GACVS. Coincidental use of oral contraceptives in this group might be confounders to the proper assessment of this vaccine safety.

**Recommendations:**
Committee awaits more data to make more conclusive statements.

**Thiazolidinediones (pioglitazone and rosiglitazone)**
Rosiglitazone has been shown to cause fluid retention and cardiac failure, myocardial ischemia, infarction and mortality. Early clinical trials showed that rosiglitazone and insulin are associated with increased risk of cardiac failure. In 2006, WHO published an analysis of spontaneous adverse drug reaction (ADR) reports from the UMC database that revealed a disproportionate increase in cardiac failure. There was a higher incidence of myocardial ischaemia (hazard ratio of 1.31) relative to comparator regimens. The information has since been added to the SPC. The US FDA meta-analysis showed increased total ischemic risk by 1.4, but the specific myocardial ischemia risk was not elevated. Significantly more women who received rosiglitazone experienced fractures of the upper arm, and or foot than women who received other drugs (this was consistent with ‘A Diabetes Outcome Progression Trial (ADOPT) study results).

Pioglitazone taken for durations of up to 3.5 years has also demonstrated an excess risk of 0.8 fractures per 100 patient years of use for women. However, the limitations of these studies were inconsistencies on mortality, the absence of increased risk of MI with combination therapy. There were other confounding issues such as control selection, selection bias. Long-term studies with pioglitazone showed a protective effect on the heart. While rosiglitazone raises blood lipids, pioglitazone increases blood lipids to a lesser extent. There may be also some hint of drug interactions between angiotensin converting enzyme (ACE) inhibitors and rosiglitazone.

There are no long-term evidence of oral hypoglycaemic agents showing real efficacy and prevention of complications. Because of the equivocal and uncertain findings from the US meta-analysis, a box warning citing uncertainty in the findings has been added. But no clear update to prescribing advice has been made.

The challenge is deciding the hierarchy of information needed to make sound regulatory decisions. There is criticism on the absence of complete efficacy-risk comparison. Regulatory decisions to allow these products in the market are based on the evidence of efficacy on lowering glycosylated haemoglobin, but long-term studies are needed to assess safety.

**Recommendations:**
Committee to consider reviewing all the evidence for further deliberations and evaluation.

**Abacavir: risk of myocardial infarction (MI)**
This issue is currently under evaluation in the EU. There seems to be an increase in risk of MI with recent use of abacavir (that is, in patients currently using or who used abacavir in the past 6 months). There is strong evidence for an emerging new signal.

A prospective study running for nine years is looking into this. But it appears that the phenomenon is also seen with didanosine. But the Glaxo post-marketing safety data appear not to have picked up this signal. A postulate is that one of the metabolites of abacavir is pro-inflammatory hence perhaps some biologic and vasculitic mechanisms are likely and should be further investigated.

**Recommendations:**
To closely follow EU decisions about this new signal.

**Biosimilars**
This session attempted to answer if drug safety profile should be linked more to the product than to the substance. The existing INN (International Nonproprietary Name) nomenclature policy will need to be changed when it comes to naming biosimilars because biologicals are not homogeneous products. For instance, Thailand has 10 epoetin alpha biosimilars, all with the INN epoetin-alfa. Eprex is an innovative epoetin, also with the INN epoetin-alpha. As a result, Eprex and the other biosimilars with the same INN are often substituted for one another at hospital pharmacies. But these have different effects. So giving a common name to all epoetins can be a big challenge in pharmacovigilance when it comes to tracing back to a substance that actually caused an adverse reaction. Some of the factors in the discussion included the dependence on the legal system of each country for classification but at the same time, encouraging the assurance of traceability of biosimilars.
Recommendations:
A sub-committee should make clarification of this issue with some proposal for clear principles of biosimilar nomenclature and the consequences of their application to PV to be taken up at the International Conference of Drug Regulatory Authorities (ICDRA).

**How to integrate vaccine definitions into the WHO Programme**
Vaccine pharmacovigilance and other related terms used were discussed. Brighton Collaboration definitions were considered for adoption. There is a need to review the WHO adverse reaction terminologies (WHO—ART), to facilitate reporting of AEFIs at national centres, and in the causality assessment of AEFIs. Some countries have separate forms for AEFI reporting and it might be useful to integrate these forms with the ADR reporting forms.

Recommendations:
Cooperation between ACSoMP and the CIOMS Vaccine pharmacovigilance working group is to be encouraged. Integration of national immunization programs with the national PV programs to be supported and strengthened. Proposal made to integrate vaccine AEFI data collection into drug ADR reporting forms and expanding UMC data fields as needed.

**How to initiate revision of existing definitions**
This session explored the context and the process for revising PV definitions; some of the definitions are old, there are emerging new terms and concepts. Examples for review are “adverse reactions”, “adverse events”, “signal”, “incidents”, “warning” and “alert.” How can patient safety be defined? Is medical error a term that needs a definition in relation to drug misuse or abuse? The session called for views and suggestions on the way forward.

There are regulatory and legal implications when revising definitions. Responsible agency to do this task needs to be identified. The Family of international Classification (FIC) or UMC could lead this initiative.

Recommendations:
The Committee agrees that definitions of terms and concepts should be reviewed. The Committee recommends that WHO takes the lead while delegating work to technical bodies.

**Optimizing use of Vigibase**
At present there are no guidelines for reporting to the Vigibase. National pharmacovigilance centres choose different criteria for submission of reports. As a consequence the database is not very consistent. All individual case safety reports collected by national pharmacovigilance centres, irrespective of the national criteria for data collection may be included in the database. Different categories of reports could be flagged and stored in a common database or separate databases could be kept for different types of reports. There may be a need to define if adverse events from food supplements and cosmetics could also be sent to the database

Recommendations:
The UMC needs to review their existing advise to national pharmacovigilance centres on what they may report to the database. An all-inclusive principle for reporting is proposed: if it affects the health of the patient, then it should be reported. UMC should draft a message to advise people on reporting requirements for drug reactions.

**Indicator-terms of drug dependence**
A project in the UMC is investigating the use of Vigibase as a resource for patient safety in areas of medication errors, interactions and drug dependence potential. Various permutations of ADR terms and cluster terms have been examined to determine if dependence signals could be picked up. There seems to be a distinction in the reporting pattern between benzodiazepines (and benzodiazepine derivatives) and other drugs known to cause dependence. For these latter drugs, it is very rare for psychiatric and other nervous system related ADR terms to be quantitatively highlighted before the term ”drug dependence” in the database. It is not clear whether these terms are predictors of drug dependence or are independent adverse events associated with benzodiazepines. Nevertheless these are clearly candidate predictors of benzodiazepine-dependence. And there are other terms which on their own may not be of predictive value but in a cluster of terms, when taken together, would predict drug dependence. Proposals are requested to find more sophisticated patterns, or other reporting trends in identifying drugs of dependence. Another approach would be a clinical review of case reports related to drug dependence. The committee is requested to advise on how to proceed.

Recommendation/action points:
The UMC internal report is to be circulated to committee members for comments. The definition of dependence/withdrawal needs to be made clear.