WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

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

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This Newsletter is also available on our Internet website:
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NEWS & ISSUES:

As usual, the WHO Pharmaceuticals Newsletter provides you with the latest safety reports, advice, warnings and other updates from regulatory authorities across the world.

In adverse events reporting, Malaysia releases record collection figures for the past year even as the WHO database, Vigibase, announces that it has surpassed 4 million case reports. To mark 50 years since the thalidomide crisis, we reprint one of the very first reports in a medical journal to raise questions about possible teratogenic adverse effects of the drug.

The Annual Meeting of National Pharmacovigilance Centres was held this year in Uppsala, Sweden. This meeting celebrated 30 years of the Uppsala Monitoring Centre, 40 years of the WHO Programme for International Drug Monitoring and 60 years of WHO. The discussions from the Working Groups at this meeting are published under Feature. A short abstract of some of the safety issues reviewed by the eighteenth meeting of the Global Advisory Committee on Vaccine Safety is also included.

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Safety of Medicines

Feature

Counterfeit medicines

Regulator tackles incident of fake Vicks Kingo

Tanzania. The Tanzania Food and Drugs Authority (TFDA) has released a statement about counterfeit cough medicine, Vicks Kingo, circulating in the market. The Agency is taking a tough line on the matter and has threatened legal action against traders.

TFDA described the counterfeit Vicks Kingo tablets as being white instead of cream coloured and said that they do not have the menthol smell of the genuine tablets. Anyone in possession of the counterfeit product is urged to return it to the suppliers and report to the nearest district or Regional Health Offices or to TFDA Zonal Offices. The statement said that "the TFDA is making a close follow-up through inspection to identify any counterfeit Vicks Kingo circulating in the market and persons proved to be dealing in supply or manufacture of the same shall be taken to court and in addition will be liable to any action for compensation if so filed by the subject".
The TFDA recently celebrated its fifth anniversary and its web site states that it aims to be Africa's best regulatory authority by 2015.

Reference:
TFDA Public announcement, 12 October 2008 (www.tfda.or.tz).

Efalizumab

Labelling changes to highlight risks of PML

USA. The United States Food and Drug Administration (US FDA) announced labelling changes, including a Boxed Warning, to highlight the risks of life-threatening infections, including progressive multifocal leukoencephalopathy, with the use of efalizumab (Raptiva).

The labelling changes are based on the US FDA's postmarketing surveillance. The Agency is also requiring the submission of a Risk Evaluation and Mitigation Strategy (REMS), which will include a Medication Guide for patients and a timetable for assessment of the REMS.
Efalizumab, approved in 2003, is a once-weekly injection approved for adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy to control their psoriasis. The drug works by suppressing the immune system to reduce psoriasis flare-ups, however by suppressing the body's immune system, it can also increase the risk of serious infections and malignancies.

Reference:
News Release, US FDA, 16 October 2008 (www.fda.gov).

Ephedrine and kava kava products

Warning against unauthorized use

Canada. Health Canada has advised consumers against using natural health products Life Choice ephedrine hydrochloride 30 mg capsules and Life Choice kava kava (kavain) 150 mg capsules. The advice came as the agency took steps to prevent these products, which have not been approved, from entering the Canadian market.

According to Health Canada, Life Choice ephedrine contains an excessive amount of ephedrine and, when taken alone or in combination with caffeine or other stimulants may lead to serious, potentially life-threatening adverse events. Furthermore, the Agency has found this product to be contaminated with bacteria, which could cause irreversible and serious adverse events, including death.

Health Canada says that kava kava-containing products have been linked to liver dysfunction. Kava kava is also associated with coordination disorders, muscle weakness and kava dermopathy (a peculiar scaly eruption on the skin).

Reference:
Media Release, Health Canada, 21 August 2008 (www.hc-sc.gc.ca).

Ergot-derived dopamine agonists

New warning on fibrosis

Europe. The European Medicines Agency (EMEA) has recommended revising the product information for ergot-derived dopamine agonists with new warnings and contraindications relating to the risk of fibrosis.

The Agency explained that although the development of fibrosis symptoms is a known adverse effect of ergot-derived dopamine agonists, new data have suggested that fibrosis may start long before the onset of symptoms. The EMEA affirmed that marketing authorizations should be maintained, but that new warnings and contraindications should be added to the relevant product information.

Ergot-derived dopamine agonists are a group of medicines that have been on the market for many years and are used to treat Parkinson's disease, either on their own or in combination with other medicines. They are also used to treat other conditions including hyperprolactinaemia, prolactinoma and to prevent lactation and migraine.

Reference:
Media Release, EMEA, 26 June 2008 (www.emea.europa.eu).

Erythropoiesis-stimulating agents

Labelling changes to clarify use / directions

USA. The US FDA has informed health-care professionals of modifications to certain sections of the Boxed Warnings, Indications and Usage, and Dosage and Administration sections of prescribing information for Erythropoiesis Stimulating Agents (ESAs). The changes clarify the US FDA-approved conditions for use of ESAs in patients with cancer and revise directions for dosing to state the haemoglobin level at which treatment with an ESA should be initiated. Additional revisions to prescribing information that ESAs are not intended for use in patients receiving myelosuppressive therapy when the expected outcome is cure and when to initiate and discontinue ESA dosing will be forthcoming.
The US FDA approved epoetin-α in 1989 and darbepoetin-α in 2001 to treat anaemia associated with chronic renal failure. Since then the indications have been expanded to include anaemia that occurs in some types of cancers.

Reference:
Follow up to the 3 January 2008 communication, US FDA (www.fda.gov).

Ezetimibe / simvastatin

Association with increased cancer risk being investigated

USA. The US FDA is reviewing the safety of the anti-cholesterol drug combination ezetimibe/simvastatin (Vytorin), after receiving a report about a possible connection between the drug and an increased cancer risk.

Preliminary results from the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial revealed that a larger percentage of ezetimibe/simvastatin (Vytorin) recipients were diagnosed with and died from cancer compared with placebo recipients, during the five year study. However, interim data from two other large ongoing trials - Study of Heart and Renal Protection (SHARP) and the Improved Reduction in High-Risk Subjects Presenting with Acute Coronary Syndrome (IMPROVE-IT) - did not show increased cancer risk with simvastatin and ezetimibe combination.
The US FDA says that it will fully evaluate the SEAS trial data and other relevant information, and has advised patients not to stop taking ezetimibe/simvastatin (Vytorin) or any other cholesterol lowering drugs until further information is available.

Reference:
US FDA, August 2008 (www.fda.gov).

Illegal medicines

Erectile stimulant Powertabs "potentially dangerous"

Switzerland. Swissmedic has announced that the erectile stimulant Powertabs, which is being sold illegally in Switzerland, contains a potentially dangerous active substance. The Agency has therefore issued an urgent warning against taking this product.

Powertabs is advertised as being a natural, purely herbal erectile stimulant. Swissmedic has analysed samples of the product, and the results have revealed that the capsules contain an active substance related to sildenafil but which has not been investigated. (Sildenafil is the active ingredient in Viagra.)

Swissmedic has already seized stocks of Powertabs from illegal sources and instigated criminal proceedings. Anyone in possession of the product is advised to destroy them or to take them to a pharmacy for destruction.

Reference:
Swissmedic, 13 August 2008 (www.swissmedic.ch).

Malaysia ADR reporting

Record figures for 2007

Malaysia. The Malaysian National Centre for Adverse Drug Reactions Monitoring has released its collection figures for 2007. The Agency had received a total of 3068 local spontaneous reports of ADRs, an increase of 20.6 per cent over the previous year.

Disorders associated with skin and appendages were the most commonly reported ADRs. The highest number of suspected cases were attributed to anti-infectives (700), followed by cardiovascular drugs (400) and analgesics (300). Perindopril, with 97 cases, was at the top of drugs with most cases, followed by allopurinol (75), cloxacillin (71), diclofenac (71), metformin (69), aspirin (67), ticlopidine (50), rifampicin (46), phenytoin (44) and amoxicillin (43).

Pharmacists and dentists sent in 1283 reports representing over 40 per cent of the total, followed by government doctors (1075), companies (409), universities (240) and general practitioners/private specialists (61).

The reporting of ADRs in Malaysia has increased steadily over the past two decades. To encourage this trend, the authorities have released results by State and a list of the top ten best reporting hospitals.

Reference:
Reactions 1121:3, 19 July 2008 (www.adisoline.com).

Vigibase

WHO adverse events database tops four million mark

Worldwide. The WHO's Individual Case Safety Reports (ICSR) database, Vigibase, has now received over four million case reports, according to the Uppsala Monitoring Centre (UMC), the WHO Collaborating Centre for International Drug Monitoring. These reports represent the concerns of health professionals around the world about possible harm caused to their patients by medicines. Currently, the UMC receives > 250 000 reports annually.

Reference:
(http://www.who-umc.org).

Genomic biomarkers

US FDA releases list for predicting drug response

The US FDA has updated a table of genomic biomarkers with established roles in drug response. These genomic biomarkers can play an important role in identifying responders and nonresponders, avoiding toxicity and adjusting the dosage of drugs to optimize their efficacy and safety. Currently, pharmacogenomic information is contained in about 10 per cent of labels for US FDA-approved drugs.

Reference:
(www.fda.gov).

Antiepileptics

Study suggests "small risks" of suicidal thoughts

UK. Any antiepileptic drug "may rarely be associated with a small increased risk of suicidal thoughts and behaviour" according to a recent Europe-wide review, published in the *Drug Safety Update* of UK's Medicines and Healthcare products Regulatory Agency (MHRA).

The review considered data from published literature, postmarketing surveillance, and a meta-analysis conducted by the US FDA, including placebo-controlled trials for 11 antiepileptic drugs among a total of 43 800 patients. An increased risk of suicidal thoughts and behaviour was found among those who received antiepileptic drugs (0.43 per cent of patients) versus those who received placebo (0.22 per cent). The increase was observed among all antiepileptic drugs studied and was evident as early as one week after starting treatment. On the basis of these findings, patients are advised to be alert to any mood changes, distressing thoughts or feelings about suicide or harming themselves during antiepileptic treatment. However, they should not stop or switch treatment without consulting a health-care professional. (See WHO Pharmaceuticals Newsletter No. 2, 2008 for related information from US FDA.)

Reference:
Drug Safety Update, 2: 2-3, 2008 (www.mhra.gov.uk).

Ceftriaxone

Fatal reactions with calcium

Canada. The antibiotic ceftriaxone should not be mixed or co-administered with calcium-containing solutions. Health Canada issued the warning to hospitals after cases of fatal reactions in neonates and infants were reported. While in most cases there was simultaneous administration of the two drugs, the interaction has been reported where ceftriaxone and calcium-containing products were given at different times and using different infusion lines.
The Agency also advises that for patients aged less than 10 weeks, intravenous ceftriaxone and calcium-containing solutions should not be administered within five days of each other. In all other patients, intravenous ceftriaxone and calcium-containing solutions should not be administered within 48 hours of each other.

Reference:
Health Canada, 31 July 2008 (www.hc-sc.gc.ca).

Lenalidomide

Adverse events associated with lenalidomide use

UK. Since being launched for multiple myeloma in June 2007, the UK MHRA has received five spontaneous reports of adverse events (AEs) associated with lenalidomide (Revlimid).
Up to 6 June 2008, the Agency had received two nonfatal reports, involving bradycardia and liver dysfunction, and three reports with fatal outcomes, involving stroke, pulmonary oedema and graft-versus-host disease. The MHRA has not received any spontaneous AE reports associated with thalidomide, which was launched in the UK in June 2008 for multiple myeloma. To date, there have been no reports involving *in utero* exposure to lenalidomide or thalidomide.

At the time of launch, lenalidomide was assumed to be a human teratogen due to its similarity to thalidomide, and both drugs are subject to risk-minimization measures including a Pregnancy Prevention Programme and dispensing restrictions. Recently, preliminary results from a study of embryofetal development in primates showed that the offspring of those receiving lenalidomide during pregnancy had developmental anomalies similar to those typically associated with thalidomide. Developmental anomalies were also seen among the offspring of control animals receiving thalidomide during pregnancy, but were not observed among the offspring of control animals that received no drugs. These early results "provide the strongest evidence to date that lenalidomide is teratogenic in primates," according to the MHRA.

Reference:
Reactions 1215:3, 16 August 2008 (www.adisonline.com).

Mitoxantrone

Multiple sclerosis patients to be monitored for cardiac toxicity

USA. All patients with multiple sclerosis who have completed mitoxantrone treatment should be monitored for late cardiac toxicity, according to the US FDA. The Agency advised that yearly quantitative evaluation of left ventricular ejection fraction (LVEF) should be carried out after patients have finished mitoxantrone treatment. This follows results of a postmarketing study which showed that for a majority of patients there had been poor compliance with recommendations added to the mitoxantrone labelling in 2005. In addition, congestive heart failure developed in four patients 4–17 months after completing mitoxantrone therapy.

The US FDA is working with manufacturers to encourage health-care professionals to adhere to the previous recommendations to evaluate LVEF before starting mitoxantrone treatment and before each dose.

Reference:
Alert, US FDA, 29 July 2008 (www.fda.gov).

Natalizumab

First cases of PML since reintroduction

USA. The US FDA has announced two cases of progressive multifocal leukoencephalopathy (PML) associated with the multiple sclerosis drug, natalizumab (Tysabri). These are the first PML cases reported since natalizumab was reintroduced* to the market in June 2006. These new cases of PML are also notable for being the first to occur in the absence of concomitant or recent immunomodulatory therapy. Both patients were receiving natalizumab monotherapy (for 14 and 17 months). One patient had a history of prior immunosuppressive therapy with azathioprine and β-interferons.

Natalizumab, a recombinant humanized monoclonal antibody, was initially approved by the US FDA in November 2004, but was withdrawn by the manufacturer in February 2005 after three patients in clinical trials developed PML.

Reference:
Alert, US FDA, 25 August 2008 (www.fda.gov).

* See WHO Pharmaceuticals Newsletter No. 4, 2006 for conditions of restricted distribution.

Nelfinavir

No increased risk of cancer with contaminated product

Europe. The risk of developing cancer is not increased among patients who received the contaminated HIV drug nelfinavir (Viracept), according to an assessment by the EMEA.

In June 2007, the EMEA recommended suspending the marketing authorization for the drug, after the detection of excess levels of an impurity, ethyl methanesulfonate (a potential carcinogen). The suspension was lifted in October 2007 after Roche, the drug's owner, provided evidence that the manufacturing problems had been resolved (see WHO Pharmaceuticals Newsletter No. 5, 2007).

As part of this decision, the Agency requested that a number of toxicological studies be conducted to assess any potential harm to patients who received nelfinavir from the affected batches.

Reference:
Media Release, EMEA, 24 July 2008 (www.emea.europa.eu).

Pyridoxine

Two cases of peripheral neuropathy

Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) has received two reports of peripheral neuropathy associated with pyridoxine (vitamin B6) products.

Recently, the country's medicines regulator, the Therapeutic Goods Administration, received a recommendation from the Complementary Medicines Evaluation Committee to amend the current warning statements required on products containing ≥ 50 mg of pyridoxine per recommended daily dose. The amendment should provide more specific advice about the symptoms of pyridoxine toxicity and should include a warning to consumers to stop taking the product if they experience burning, numbness or tingling and to see a health-care provider as soon as possible.

Reference:
Australian Adverse Drug Reactions Bulletin, 27:14-15, 2008 (www.tga.gov.au).

Simvastatin / amiodarone

Combination increases rhabdomyolysis

USA. The US FDA has issued an alert notifying the public of an increased risk of rhabdomyolysis when simvastatin is used in combination with amiodarone. The risk of developing rhabdomyolysis is dose-related, and increases when a dose of simvastatin > 20 mg/day is given with amiodarone.

The labelling for simvastatin was previously revised in 2002 to describe an increased risk of rhabdomyolysis with simvastatin doses of > 20 mg/day when taken in conjunction with amiodarone. However, the US FDA has continued to receive reports of rhabdomyolysis among patients who have been treated concurrently with amiodarone and simvastatin, particularly with simvastatin doses > 20 mg/day. Rhabdomyolysis, a rare condition of muscle injury, can lead to kidney failure or death.

Reference:
Alert, US FDA, 8 August 2008 (www.fda.gov).

Temsirolimus

Cancer drug linked to infusion reactions

Canada. Wyeth Pharmaceuticals and Health Canada have warned of the risk of hypersensitivity/ infusion reactions with temsirolimus. Health-care professionals are advised that patients be premedicated with a selective H_1-receptor antagonist before starting intravenous temsirolimus.

Forty-six medically confirmed reports of hypersensitivity/infusion reactions of varying severity associated with temsirolimus have been reported worldwide. These reactions were life threatening in six cases and fatal in one. Of 39 reports with dose-time information, 25 occurred with the first dose, often within the first few minutes of the infusion. However, hypersensitivity reactions have also been associated with subsequent infusions. Other related adverse events including loss of consciousness, apnoea, dyspnoea, hypotension, chest pain and flushing have been reported in association with temsirolimus.

Reference:
Media Release, Health Canada, 11 August 2008 (www.hc-sc.gc.ca).

Varenicline

Postmarketing data leads to warning over suicidal thoughts

UK. The MHRA has advised that patients should stop taking the anti-smoking medicine varenicline and contact their doctors if suicidal thoughts or behaviour and mood changes occur. This follows the Agency's announcement that it had received 129 reports of suicidal thoughts or behaviour associated with varenicline use. Varenicline was launched in the UK in December 2006 and by March 2008, about 366 000 people had received the drug. The events reported to the MHRA included completed suicide (2 events), attempted suicide (4), suicidal behaviour (4), suicidal ideation (118) and suicidal depression (5), with more than one event reported in some varenicline recipients. According to the MHRA, most of these reports involved people with psychological risk factors or pre-existing psychiatric conditions. However, suicide-related events have been reported in varenicline recipients with no pre-existing psychiatric conditions and in those who continued to smoke. (See WHO Pharmaceuticals Newsletter No. 3, 2008 for neuropsychiatric events reported with varencline (Champix) in Canada.)

Reference:
Drug Safety Update, 1: 2-3, 2008 (www.mhra.gov.uk).

US FDA unveils new safety web page

USA. Patients and health-care professionals can now go to a single page on the FDA web site for drug safety information. According to Paul Seligman, associate director of Safety Policy and Communication in the US FDA's Center for Drug Evaluation and Research "by placing web links to these up-to-date resources on a single page, we're helping consumers and health-care professionals find drug safety information faster and easier".
The new web page includes various links to postmarketing drug safety information to improve transparency and communication to patients and health-care providers.

Reference:
(www.fda.gov).

REMEMBERING THE THALIDOMIDE DISASTER

Fifty years ago, the world witnessed a shocking adverse event associated with the use of thalidomide, when the first phocomelia baby was delivered by a mother who had taken thalidomide during her pregnancy. Below we reprint one of the very first reports on teratogenic adverse events related to the drug.

Thalidomide and congenital abnormalities

SIR,

Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in the structures developed from the mesenchyme – i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales W. G. McBride

In our issue of Dec.2 we included a statement from the Distillers Company (Biochemicals) Ltd. Referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the foetus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide. – Ed.L

Reference:

McBride WG, Thalidomide and congenital abnormalities, Lancet, 2:1358, 1961.

Eighteenth Meeting of the Global Advisory Committee on Vaccine Safety 18–19 June 2008

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was established by WHO in 1999 to respond promptly, efficiently and with scientific rigour to vaccine safety issues of potential global importance. Issues described by the Committee during its eighteenth meeting, held on 18-19 June in Geneva, Switzerland, included the safety of yellow fever vaccine, mitochondrial diseases and vaccination, and thiomersal.

Safety of yellow fever vaccine

The Committee was updated on evidence regarding the safety of 17D yellow fever vaccines. It focused primarily on four fatal cases and one non-fatal case of vaccine-associated viscerotropic disease (YEL-AVD) occurring among 63 174 individuals vaccinated in the Ica Region of Peru following a yellow fever vaccination campaign conducted in September-October 2007 after a major earthquake. All five cases received vaccine from the same lot. The incidence of YEL-AVD (estimated as 11.7/100 000 vaccinated based on the number of people receiving the vaccine lot or 7.9/100 000 based on all those vaccinated in the Ica Region) was noted to be more than 20 times higher than the risk previously associated with 17D vaccines in general.

Following review of the data collected during the investigation, the Committee concluded that the cause of the cluster of cases was not clear. One of the cases presented a known risk factor; a second case presented a potential risk factor. Tests showed that the lot administered met all quality specifications and the yellow fever virus isolated from three confirmed cases was consistent with the vaccine virus and did not appear to have mutated. Approximately 72 000 doses of the vaccine lot common to the YEL-AVD cases was confirmed to have been used elsewhere in Latin America without additional cases of YEL-AVD.

The GACVS reiterated the need to obtain better estimates of rates of serious adverse events and to be better able to predict which individuals are at risk for such events. Members indicated support for the initiatives of WHO and other global partners in these areas.

Mitochondrial diseases and vaccination

The GACVS reviewed the limited data on mitochondrial disorders and vaccination available from the United Kingdom of Great Britain and Northern Ireland and the United States. The Committee concluded that there is no convincing evidence to support an association between vaccination and deterioration of mitochondrial diseases (inherited disorders of energy metabolism that tend to affect tissues with high energy requirements such as the brain, heart and liver). The topic will be reviewed further if new findings become available. GACVS supports continued vaccination of children with mitochondrial diseases with the same vaccines as are given to healthy children.

Thiomersal

The Committee reviewed a recently-published pharmacokinetic study of mercury in premature and low-birth-weight infants who received a birth dose of hepatitis B vaccine containing thiomersal, and the results of a study conducted in Italy that examined neuropsychological performance 10 years after immunization in infancy with thiomersal-containing vaccines.

On the basis of the presented data, GACVS remains of the view that there is no evidence to support a change in WHO's recommendations for thiomersal-containing vaccines and the vaccination of low-birth-weight infants where indicated.

Other topics discussed during the meeting were: diphtheria-tetanus-pertussis (DTP) vaccine and asthma; non-specific effects of DTP vaccine on child mortality; and inadvertent administration of rubella vaccine to women shortly before or during pregnancy.

The report of the meeting was published in the WHO Weekly Epidemiological Record on 8 August 2008 and has been posted on the GACVS web site at http://www.who.int/vaccine_safety/en.

Thirty-first annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring 20-23 October 2008

There were eight breakout sessions at the recently concluded annual meeting of pharmacovigilance centres in Uppsala, Sweden. Below is a summary of recommendations and discussion points from the working groups at these sessions.

1. The need for new and updated definitions in pharmacovigilance

One of the reasons to revisit pharmacovigilance definitions is that some of the definitions are old, there are new terms and concepts surfacing. Examples for review are "adverse reactions" and "adverse events" and "signal", "incidents", "warning" and "alert." How can patient safety be defined? Is medical error a term or a concept that needs a definition in relation to drug misuse or abuse?

The working group in 2008 discussed whether there is the need to change the WHO definitions of pharmacovigilance and adverse drug reactions. The consensus was "no" for the definition of pharmacovigilance, and "maybe " for the definition of adverse drug reactions because it could be better to be more patient-oriented.

It was recommended that we consider and harmonize the definitions of the PV terms, including: adverse drug reaction, adverse drug event, signal, medication error, seriousness, and severity. In relation to this, we also need to think of translations.

2. Indicators for measuring development and impact of pharmacovigilance

The working group addressed the following questions: do we need indicators for pharmacovigilance? What sort of indicators do we need? How do we develop them?.

It was agreed that pharmacovigilance indicators need to be developed for measuring development and impact of pharmacovigilance, which has expanded greatly in the last 50 years. The pharmacovigilance indicators could become an advocacy tool and be used for resource mobilization. These indicators should be simple to understand and measure, reproducible, sensitive enough to detect pharmacovigilance problems, and robust. Many types of indicators would be needed, including structural indicators, process indicators and outcome (impact) indicators. The impact indicators are difficult to come up with, but very important for advocacy to policy makers. The working group members would provide comments by email by the end of November 2008 to generate a minimum (core) set of indicators and a supplementary list of indicators. These indicators could be presented to the next WHO Advisory Committee on Safety of Medicinal Products.

It was recommended that WHO should facilitate further the process of developing indicators.

3. Towards a global approach for vaccine crisis management

In this working group, the key elements for a global crisis management strategy under development by WHO were presented, followed by discussion. The WHO approach is aimed at establishing a strategy for the effective management of vaccine safety crises of potential or known global importance. The development of the strategy consists of the following steps: a review of the management of past vaccine safety crises, identifying specific challenges for responding effectively to crises, defining main stakeholders and roles, defining the mechanisms and resources specific to managing vaccine safety crises and to implement the strategy. WHO plans to conduct consultations internally and with stakeholders before the strategy is finalized.

Group discussion focused on two questions: What are the gaps at country level in managing vaccine safety crises that could be addressed by a global strategy? Are there any gaps in the global approach as currently presented that should be addressed?

The WHO approach was generally agreed upon. In addition, the following points were made: a proactive approach to vaccine safety surveillance should include efforts to ensure proper use of vaccine, need for "preparedness" in order to optimize response to safety issues, need for good "filter" for vaccine safety issues as concerns may be "old news" still circulating, sources of information must be considered in identifying issues, conflict of interest

needs to be considered if an agency promoting immunization is also the one that monitors safety, pharmacovigilance must promote issues from the user's point of view, and tools for countries to assess AEFI concerns would be appreciated.

4. Trends in the safety of herbal medicines

The use of herbal medicines is a growing phenomenon in both developed and developing countries. To improve patient safety, various WHO-led initiatives encourage Member States to establish comprehensive national pharmacovigilance systems which incorporate herbal medicines. The unique characteristics of herbal medicines pose enormous challenges to monitoring of the safety of herbal medicines effectively. After years of implementation of various measures by national regulatory authorities and national pharmacovigilance centres, it is appropriate to assess the effectiveness of those approaches.

The objectives of this working group were: 1) to share recent observations related to herbal medicines' safety concerns, 2) to identify better ways to apply the WHO guidelines and other technical documents to enhance safety of herbal medicines, 3) to identify means of creating trust among health professionals, providers of herbal medicines and patients for the prevention of potentially serious risks from misuse of herbal medicines, 4) to propose tools for assessment of the effectiveness of national pharmacovigilance systems for monitoring of herbal medicines, and 5) to make recommendations to WHO about specific technical assistance to national centres.

Discussions for the objectives from 1 to 5 include the following:

The group agreed to distinguish the differences between "herbal medicines" (referring to herbal products regulated as medicines under national regulatory framework) and "herbal remedies" (referring to herbal products not regulated as medicines under the national regulatory framework and herbal preparation directly given by the practitioners, e.g. traditional medicine practitioners, and herbalists).

1) Proliferation on the market of developing countries of herbal remedies and the so-called food supplements adulterated with undeclared pharmaceutical substances (orthodox medicines) pose a serious threat to patient safety. Patient safety continues to be compromised by the misconception that every natural product is safe. In the absence of a regulatory framework for herbal medicines in most of these countries, it is almost impossible to implement any effective regulatory intervention including adverse drug reaction monitoring of herbal medicines. It was also pointed out that the traditional medicine practitioners or herbalists in these countries provide their own herbal formularies directly to their patients as part of their practice and that these herbal formularies are usually not the subject under the national regulation. It is difficult to regulate such products particularly in these developing countries. It was suggested that the establishment of a national regulatory framework for registration of traditional medicine practitioners or herbalists may be one approach to improve the situation.

2) The group acknowledged the availability of WHO guidelines and other documents which could be applied not only to guide regulation of herbal medicines and the monitoring of their safety, but also to provide training. However, there appear to be cases where these resource materials are kept in offices without being utilized in those countries where herbal remedies are on the market.

3) The low numbers of spontaneous adverse drug reaction reports associated with herbal medicines were attributed to the general lack of "pharmacovigilance culture" among stakeholders. For trust, transparency is necessary and there must be the willingness by both producers of herbal medicines and providers of herbal medicines, especially traditional practitioners to learn proven ways of doing things better and to observe regulatory requirements and best practices. A herbal remedy that has been subjected to the necessary scientific assessment and is duly registered induces confidence for its use and for its safety profile to be better monitored.

4) In principle, it was recognized that there is the need for the assessment of the effectiveness of a pharmacovigilance system for monitoring the safety of patients who use herbal medicines. It was, however, observed that until the necessary legislative and regulatory framework and the accompanying infrastructure are put in place, it is practically impossible to define the required assessment tools.

5) Since countries are at various levels of regulatory "maturity" in respect of the regulation of herbal medicines, it was the opinion of the group that national centres and national regulatory authorities should identify their specific needs to be presented to their respective governments and WHO.

It was recommended that governments should exercise the political will to put in place the necessary legislative framework for the effective regulation of herbal medicines. National regulatory authorities and pharmacovigilance centres should make use of available resources including the WHO guidelines and other published texts to enhance their regulatory processes and safety monitoring efforts. WHO, in collaboration with national centres, should take the lead in the creation of training opportunities for providers of herbal medicines to improve their knowledge base in quality issues in general and to introduce them to the culture of pharmacovigilance in particular to enhance spontaneous reporting by providers of herbal medicines. Countries should strengthen the capacity of their quality control infrastructures to analyse herbal medicines and the so-called food supplements, and to share such information.

Discussion
For effective therapeutic and ADR monitoring of herbal medicines, the labels of products should indicate the place of origin in order to identify the drug properly.

5. Acting on pharmacovigilance data for better decisions on benefit and harm
Spontaneous reporting of ADRs is the mainstay of pharmacovigilance. Signals from spontaneous reporting and analysis of individual case safety reports are increasingly being used for regulatory decisions, even though spontaneous reporting is often challenged as being scientifically weak.

This working group discussed the following points: how safe is "safe"? How much level of evidence is required for regulatory decision and action? Making in-country decisions on market withdrawal of a product based on actions of other countries, balancing benefit for a small patient population with potential harm to the rest of the population, global imbalance in evidence, important factors to be considered in risk decision-making, global variations in decisions of drug regulatory authorities, risk in mass prevention campaigns, communicating to patients, data-mining of the UMC database to stratify signals by region, promotional tactics of marketing authorization holders, the need for collaboration with the industry, issues of withdrawal for commercial reasons, the need for more PV methods and tools such as qualitative methods and pharmacogenetics, modelling for decision making processes, referring to risk assessment models from other industry and fields, importance of the involvement of PV experts early in the drug development and licensing process, and importance of continuing training and education on risk and benefit analysis. Currently there is no standard guidance for regulatory authorities for making decisions based on pharmacovigilance data. Each case is discussed on an ad hoc basis. The 1998 CIOMS publication 'Benefit-Risk balance for Marketed Drugs: Evaluating Safety Signals' was discussed. It was agreed that this publication should be revisited and simplified in order to provide guidance for regulatory authorities throughout the world on decision-making.

6. Special training needs to promote patient reporting
Not all countries acknowledge patient reporting, this is especially true for the developing countries. In countries where patient reports are accepted, the experiences are positive. The quality of patient reports is equal to that of other reporters. Different means of reporting such as telephone, Internet and paper form were discussed. However, in some countries these means are not feasible because of lack of resources and illiteracy. In these countries it was suggested that the patient could report via an intermediate who can be a nurse or a pharmacist. However, this will hamper the unfiltered information that patients provide when filling in the form themselves. It was also touched upon how the reports should be assessed and stored. In the countries that accept patient reporting, the reports are coded as all other reports and stored in the same database as other reports. The best way to promote patient reporting would be through education and collaboration with a patient organization. It is important to realize that the patient might have other expectations than health professionals when they report, so the pharmacovigilance centre has to prepare for this. Australia, the Netherlands and Sweden offered to continue the work of this group in the year to come.

Discussion
The role of patient-reporting can be different depending on how pharmacovigilance is integrated in the health-care system. It was suggested to add someone from a developing country and someone from Morocco, which is heading the Patient Safety pilot project, to the working group.

7. Better use of national databases for intensive analysis of case reports

The size of national databases ranges from a few hundred to a million case reports and more countries are starting to build up a database with case reports, which is an encouraging trend.

The questions this working group discussed were: how many reports of an individual drug/ADR combination are needed in a database before we start investigating a problem related to a drug? How is information sorted in a database to identify potential problems? What actions should be taken when an unknown problem is identified in the database?

With regard to the first question, it was agreed that there is no minimum number of reports. It depends on the seriousness of the ADR, risk-benefit profile for that drug, temporal causal relationship between the drug and ADR, and expectedness of the ADR. There are other factors to be considered, for example, information on denominator, quality of reports and source of report (whether consumer reports should be identified differently from reports from health-care professionals in a database). For causality assessment, it was suggested that education for individual assessors to build up knowledge on how to assess a report be included in VigiFlow training. With regard to the second question, in routine screening, different methods of sorting and analysis can be applied depending on frequency of reports, expectedness of ADR, and other factors. Automated data-mining is not essential unless the size of database is very large. With regard to the last question, possible actions could be to take appropriate measures at a prescriber and regulatory level if there are sufficient data in a single database, and to discuss the issue with specialists if clinical uncertainty has been identified. The supporting information can be sought in neighbouring countries with similar populations, Vigimed, Vigibase and other sources. It was agreed that there could be more efficient detection of unknown ADR by collaborating with other countries.

In addition, the group considered collaboration with UMC to search for reports in Vigibase (WHO ICSR database) to increase efficiency of signal detection if there are not enough index cases in the national database. In this regard, the group also identified possible barriers such as the limitation of information and delay of inclusion of reports in Vigibase. To solve the barriers, it was suggested to speed up inclusion of reports.

8. Implementing strategies for medication errors

This working group discussed the following issues: 1) How to collect reports of Medication Errors? Should the same reporting form be used for ADRs and medication errors? Are additional fields required to facilitate reporting of medication errors? 2) Who should take responsibility for reporting medication errors? What contribution should national monitoring centres make in identifying and addressing medication errors? 3) Regional or centralized approach to addressing medication errors? How can a network be developed? 4) How can reporting of medication errors be encouraged? How can the issue of liability be addressed? What responsibility does the national monitoring centre have when they receive a report?

In response to these questions, the following points were made on the role of National Centres in addressing medication errors, reporting systems, liability and responsibility, definitions, and possible pharmacovigilance activities.

For National Centres to address medication errors, networks which allow collaborative input from all stakeholders should be developed. National Centres should interact with relevant national bodies to ensure integration of activities related to medication errors. For reporting, the current reporting system should be enhanced to capture medication errors. Building on existing reporting systems is considered to be the most cost-effective approach. To detect medication errors, generally high quality reports are required. In order to address fears of liability it is important to communicate clearly that the purpose of collecting data on medication errors is to prevent patients suffering preventable adverse events, not for punishment. Pharmacovigilance definitions relating to medication errors should be developed and/or clarified, given that medication errors would be related to the use of the product rather than to the property of the drug. Pharmacovigilance programmes are well-placed to react to medication errors and highlight high-risk medicines. International collaboration with data sharing and consequential development of guidance would also be useful.

In conclusion, pharmacovigilance is now considering patient safety rather than just medicine safety and there is a need to address medication errors in this context. Educational initiatives are necessary to promote high quality reports for detection of medication errors.

Discussion
It was mentioned that a pilot project with focus on medication errors was ongoing at the Morocco PV National Centre. WHO expects that some framework would be established and circulated in the future, based on current work.

New guidance for communicating health risks

Canada. Health Canada has released guidance on how to communicate health risks about medicines marketed in the country.

In Canada, when a health risk occurs with a medicine, Health Canada or the Market Authorization Holder (MAH) have to consider issuing one or more of 13 risk communication documents. The guidance provides information on the documents and describes the situations where Health Canada or the MAH should consider communicating the risks.

The guidance builds on the principles established in Health Canada's Strategic Risk Communications Framework, which emphasizes a strategic, systematic approach to effective communication. The Agency said it will continue to evaluate its guidance and find ways to improve the methods used to communicate health risks.

Reference:
(www.hc-sc.gc.ca).

Correction
The following reference (web site of the Health Sciences Authority in Singapore) replaces the previous reference (www.dh.gov.hk) for 'Singapore reporting (2007)' on page 12 of WHO Pharmaceuticals Newsletter No. 3, 2008.

Correct Reference: www.hsa.gov.sg