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News & Issues

This is the last issue for the year. We include regulatory and safety information on medicines, information on some new publications as well as the working group recommendations from the Twenty-ninth Annual Meeting of Representatives of the National Centres participating in the WHO Programme for International Drug Monitoring.

In 2006, the Quality Assurance and Safety of Medicines team was kept busy with its prequalification project, standards and normative work for quality pharmaceuticals and pharmacovigilance issues: 44 medicines were 'prequalified'; the fourth edition of the WHO International Pharmacopoeia was published; the INN advisory group for the nomenclature of biologicals was established; the total number of member countries in the WHO Programme for International Drug Monitoring increased to 98; the Expert Committee on Drug Dependence had its thirty-fourth meeting; the International Working Group for Drug Statistics Methodology met twice; numerous training courses were carried out and the International Medical Products Anti-Counterfeiting Taskforce (IMPACT) was established. These were some of the highlights, all of which are important in our progress towards achieving the millennium development goals (<http://www.un.org/millenniumgoals/>).

In the year 2007 the Safety team will continue to focus on public health programmes, with renewed emphasis on capacity building in pharmacovigilance.

We wish all our readers a very happy and fulfilling year in 2007.

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Adalimumab, etanercept, infliximab

Previous HBV infection to be evaluated

New Zealand. Medsafe, the New Zealand Medicines and Medical Devices Safety Authority is notifying health-care professionals that hepatitis B virus (HBV) reactivation has been reported internationally in patients receiving tumour necrosis factor antagonists (anti-TNF) etanercept (Enbrel), adalimumab (Humira) and infliximab (Remicade). In the majority of these reports patients were also receiving concomitant treatment with other immunosuppressants, confounding a clear causal relationship between HBV reactivation and TNF antagonists. However, Medsafe is advising that patients who are at risk for HBV infection should be evaluated for prior HBV infection before TNF antagonist therapy is initiated; those who are carriers of HBV infection should be closely monitored for HBV reactivation during TNF antagonist therapy and for several months after therapy termination. TNF antagonists should be stopped, and effective antivirals and appropriate supportive treatment should be initiated in patients who develop HBV reactivation. According to Medsafe, the New Zealand data sheets for the relevant anti-TNF products (Remicade, Humira and Enbrel) have been updated to include this safety information.

Reference:

'Dear Health-care Professional' letter from New Zealand Medicines and Medical Devices Safety Authority (Medsafe), 8 November 2006 (www.medsafe.govt.nz).

Dextro-propoxyphene-paracetamol combination products

Risk of overdose; updated prescribing information

New Zealand. The prescribing information for dextropropoxyphene/paracetamol (acetaminophen)-containing products (Capadex and Paradex) has been updated in New Zealand to manage the risks associated with these products. In 2005, the Medicines Adverse Reactions Committee (MARC) and Medsafe reviewed the risk of overdose associated with dextropropoxyphene/paracetamol-containing products (like Capadex and Paradex) after deaths were reported following intentional and accidental overdose. Several changes have been made to the prescribing information for these products (Capadex and Paradex), which include:

- narrowing of the indication to the relief of chronic pain of moderate severity;
- restriction to second-line therapy for patients who have not tolerated, or have inadequately responded to therapeutic doses of alternative analgesics;
- restriction of the recommended dose to two tablets up to every four hours, with a maximum daily dose of eight tablets (equivalent to paracetamol 2.6g);
- reducing dose in the elderly and in patients with renal or hepatic impairment.

Medsafe has urged prescribers to avoid the concurrent use of these products with alcohol or with other paracetamol-containing products, and to warrant caution while prescribing them in patients

receiving anxiolytics or antidepressants. (Reports in WHO database: Death -10).

Reference:

Prescriber Update, Vol 27(2): 21, 2006 (www.medsafe.govt.nz).

Dopamine agonists

Increased libido, gambling: class effects

Europe. A European Review has concluded that pathological gambling and increased libido including hypersexuality may be class effects of all dopamine receptor agonists. New wording has now been recommended for all products containing dopamine receptor agonists. According to the Public Assessment Report for dopamine agonists (available on the UK Medicines and Healthcare products Regulatory Agency (MHRA) website):

- cases of pathological gambling have been reported for bromocriptine, cabergoline, pergolide, pramipexole, pramipexole, quinagolide and ropinirole; this is also a recognized adverse reaction with the new dopaminergic drug rotigotine;
- although there were no reports of pathological gambling in patients taking levodopa monotherapy, levodopa may have attributed to the development of pathological gambling in patients receiving combination therapy;
- cases of increased libido have also been received for levodopa, apomorphine, bromocriptine, cabergoline, pergolide, pramipexole, pramipexole, quinagolide and ropinirole;
- both spontaneous observations and literature cases support a temporal relationship with reports of pathological gambling after starting dopaminergic drug therapy and with recovery after drug withdrawal;

- spontaneous reports and literature cases also support a temporal association between dopamine agonists and increased libido, with evidence of increased libido after starting therapy or following an increase in the dose of the dopamine agonist; positive dechallenge and rechallenge data also exist for these effects;
- no reports have been identified of pathological gambling, increased libido, or hypersexuality in association with α -dihydroergocryptine and lisuride.

The European Pharmacovigilance Working Party has concluded that both pathological gambling and increased libido, including hypersexuality, may be class effects of dopamine agonists and should be included in the Summary of Product Characteristics (SPC) for all dopamine agonists.

Reference:
Public Assessment Report - dopamine agonists, 7 November 2006 (www.mhra.gov.uk).

Imatinib

Prescribing information revised for cardiac effects

USA. Novartis US has issued a 'Dear Health-care Professional' letter (1) regarding the severe congestive heart failure and left ventricular dysfunction in patients treated with imatinib (Gleevec) used in the treatment of chronic myeloid leukaemia. The letter provides information about imatinib (Gleevec) and refers to an article published in *Nature Medicine* (2) that reported severe congestive heart failure and ventricular dysfunction in 10 patients receiving imatinib (Gleevec). Novartis points out that most of these 10 patients had pre-existing conditions such as hypertension, coronary artery disease and diabetes. Since publication of this article, Novartis has further evaluated all available data from spontaneous reporting and clinical trials. The company

concludes that "while cardiac events remain uncommon, severe congestive heart failure and left ventricular dysfunction have occasionally been reported". The company advises that patients with known cardiac disease or risk factors for heart failure should be carefully monitored while on imatinib, and those with symptoms of heart failure should be evaluated and treated. Novartis advises that the Precautions Section of the imatinib (Gleevec) prescribing information has been revised accordingly.

(Reports in WHO database: Cardiac failure - 20).

References:

1. 'Dear Health-care Professional' letter from Novartis Pharmaceuticals Corporation, 19 October 2006 (www.fda.gov).
2. Kerkela R, Grazette L, Yacobi R et al. Cardiotoxicity of the cancer therapeutic agent imatinib mesylate. *Nature Medicine*, 2006, 12(8): 881-882.

Oseltamivir

Prescribing information updated with neuropsychiatric events

USA, Canada. The prescribing information for oseltamivir (Tamiflu) has been updated in the US (1) for neuropsychiatric adverse events reported during the post-marketing clinical use of the drug. Roche Laboratories Inc., the Marketing Authorization Holder for oseltamivir (Tamiflu) in the USA has revised the product information with the following: 'Precautions/Neuropsychiatric Events: There have been post-marketing reports (mostly from Japan) of self-injury and delirium with the use of oseltamivir (Tamiflu) in patients with influenza. The reports were primarily among paediatric patients. The relative

contribution of the drug to these events is not known.' The revised information also states that people with flu, particularly children, may be at an increased risk of self-injury and confusion shortly after taking oseltamivir (Tamiflu) and should be closely monitored for signs of unusual behaviour.

Health Canada has issued a Public Information Update (2) for the above post-marketing events and has requested the manufacturer, Hoffman-La Roche to update the Canadian prescribing information for oseltamivir (Tamiflu).

(Reports in WHO database: Delirium - 5).

References:

1. 'Dear Health-care Professional' letter from Roche Laboratories Inc., 13 November 2006 (www.fda.gov).
2. Information Update. Health Canada, 29 November 2006 (www.hc-sc.gc.ca).

Rituximab

Bowel obstruction and gastrointestinal perforation

Canada. Hoffman-La Roche Limited, in consultation with Health Canada, has issued a 'Dear Health-care Professional' letter (1) and a Public Communication (2) with new safety information on rituximab (Rituxan). Post-marketing reports of abdominal pain, intestinal obstruction, gastro intestinal (GI) perforations and death have been observed in patients receiving rituximab (Rituxan), a recombinant monoclonal antibody indicated for the treatment of B-cell Non-Hodgkin's Lymphoma (NHL) and Rheumatoid Arthritis (RA). According to Roche,

- the pharmacovigilance database for rituximab (Rituxan) contains 47 cases of bowel obstruction (nine deaths) and 37 cases of GI perforations

(four deaths), based on about 730 000 patient exposures; these cases include reports from spontaneous sources as well as clinical studies;

- the majority of these events have occurred in patients receiving rituximab (Rituxan) in combination with chemotherapy for NHL;
- interpretation of data for most of the cases of bowel obstruction was confounded by the presence of multiple risk factors, including GI lymphoma, various other GI disorders and concomitant treatments, such as chemotherapy, steroids, and radiation therapy; despite these, a contributory role of rituximab (Rituxan) in causing GI perforations has not been excluded;
- the mean time to onset of symptoms was six days from rituximab (Rituxan) initiation in patients with NHL who developed GI perforations.

The Canadian Product Monograph for rituximab (Rituxan) has been updated to include the above information. In its Public Advisory, Roche says that intestinal obstruction and GI perforations "are serious conditions that require immediate medical attention". The company has advised patients to immediately contact their physicians if they experience abdominal pain, nausea, vomiting, constipation or diarrhoea, abdominal swelling, abdominal tenderness, high fever, chills or any other unusual symptoms during rituximab (Rituxan) treatment.

(Reports in WHO database: Intestinal obstruction - 8; Abdominal pain - 84; Death - 100).

References:

1. 'Dear Health-care Professional' letter from Hoffman-La Roche Limited, 10 November 2006 (www.hc-sc.gc.ca).
2. Public Communication. Health Canada, 10 November 2006 (www.hc-sc.gc.ca).

Rotavirus vaccine

For oral administration only

Europe. GlaxoSmithKline (GSK) has written to health professionals that the rotavirus vaccine (Rotarix) should be administered orally. The company points out that unlike most other vaccines, rotavirus vaccine (Rotarix) is given orally, with an applicator that resembles a syringe. GSK has received 20 reports worldwide describing the wrong route of administration of this vaccine when it was injected intramuscularly or subcutaneously. The company says there have been six non-serious adverse events reported from outside the European Union in association with the improper route of administration of the rotavirus vaccine (Rotarix). These reports described reactions that were mild, such as local erythema. All reactions were reported on the day of vaccination and did not persist beyond 24 hours. GSK is reinforcing the product information and labelling accordingly.

Reference:

'Dear Doctor' letter from GlaxoSmithKline (Vaccines), October 2006 (www.mhra.gov.uk).

Benzocaine (local anaesthetic)

Risk of methaemoglobinaemia

Canada. A Health Canada Advisory is warning Canadians about a link between the local anaesthetic benzocaine and a potentially serious blood condition known as methaemoglobinaemia (MHb). Benzocaine is a topical anaesthetic used to numb the skin or mucous membranes in surgical, dental and other medical procedures. MHb, an adverse reaction known to be associated with benzocaine, reduces the ability of red blood cells to deliver oxygen throughout the body. MHb can lead to stupor, coma and death. To date, Health Canada has received reports of nine cases of suspected MHb associated with the use of benzocaine. None of the cases were fatal. All cases of benzocaine-induced MHb have been associated with high-concentration (14 - 20 per cent) spray forms of the product used on mucous membranes during various medical procedures. Health Canada warns that infants as well as individuals with pre-existing mucous membrane inflammation or damage, with heart disease, suffering from malnutrition or with specific conditions (e.g. G6PD deficiency) are at increased risk. Health Canada will issue a notice to hospitals to remind health-care professionals about this adverse reaction and will recommend ways to minimize the risk.

Reference:

Advisories, Warnings & Recalls.
Health Canada,
24 November 2006
(www.hc.sc.gc.ca).

Cholesterol lowering drugs Linked with psychiatric reactions

New Zealand. The Centre for Adverse Reactions Monitoring (CARM) in New Zealand has been receiving an increasing number of reports of psychiatric reactions occurring with fibrates, statins and ezetimibe. These reports account for up to one-fifth of the total adverse reaction reports for some of these agents. Of particular concern are reactions of aggressive behaviour. Other notable reactions include memory impairment, mood, cognitive and sleep and perception disorders. Medsafe advises prescribers to consider cholesterol-lowering drugs as a potential causal explanation in patients who present with psychiatric symptoms.

Reference:

Prescriber Update,
Vol 27(2): 18, 2006
(www.medsafe.gov.nz).

Ezetimebe Reports of depression

Australia. There are 265 reports of suspected adverse reactions associated with the use of ezetimibe in Australia. The Australian Adverse Drug Reactions Advisory Committee (ADRAC) notes that twelve of these reports describe depression (9) or depressed mood (3) in patients aged 60 to 82 years. In all cases, ezetimibe was the sole suspected drug. Symptoms occurred rapidly, within four days in seven of the reports and at four to six weeks in another three. In five patients, symptoms resolved on withdrawal of ezetimibe but recurred on rechallenge. In general, the pattern of reporting suggests a possible causal relationship between ezetimibe and depression, particularly in the elderly, in the early phase of treatment.

ADRAC advises that reports of depression/depressed mood, as a proportion of total reports received, are higher for ezetimibe. At present there is no mention of depression in the product information for ezetimibe (Ezetrol). ADRAC will continue to monitor reports of depression associated with ezetimibe treatment.

Reference:

Australian Adverse Drug Reactions Bulletin,
25 (5): 19, 2006
(www.tga.gov.au).

Ezetimebe Reports of muscular disorders

New Zealand. Medsafe warns that ezetimibe (Ezetrol, also Vytorin, which contains ezetimibe with simvastatin) has the potential to cause myopathy or rhabdomyolysis. Ezetimibe, used in the management of hypercholesterolemia, can be given alone or with a statin. Among the 44 reports of suspected adverse reactions to ezetimibe received up to 30 June 2006 at CARM, there were nine reports of myalgia, one report of suspected myopathy, and one report of myalgia and muscle weakness. Six patients were not taking a fibrate or a statin, both of which are known to cause muscle disorders. Four of these patients recovered when ezetimibe was discontinued. Medsafe advises prescribers to be alert to the risk of myopathy (including rhabdomyolysis) with ezetimibe and to immediately discontinue treatment with ezetimibe if myopathy is diagnosed or suspected.

(Reports in WHO database: Myopathy - 94 (since 2003); Rhabdomyolysis - 108 (since 2003)).

Reference:

Prescriber Update,
Vol 27(2): 19, 2006
(www.medsafe.gov.nz).

Meningococcal conjugate vaccine

Update on reports of Guillain Barré syndrome

USA. According to a statement by the United States Food and Drug Administration (US FDA) and Centre for Disease Control and Prevention (CDC), the US Vaccine Adverse Event Reporting System has (until 20 October 2006) received 17 reports of Guillain Barré syndrome (GBS) following the administration of the meningococcal conjugate vaccine A, C, Y, and W-135 (trade name Menactra). Of these, 15 cases involved individuals aged 11–19 years who developed GBS within six weeks of receiving the vaccine (Menactra); two cases were reported in individuals 20 years of age and older. All individuals are reported to be recovering or have recovered. According to the FDA it is not clear whether the vaccine (Menactra) increases the risk of GBS. Current data suggest a possible increase of about 1.25 GBS cases for every million vaccinees. Additional larger studies are planned to provide a more definitive assessment.

Reference:

Statement. U.S. Food and Drug Administration, 20 October 2006 (www.fda.gov).

Methadone

Use for pain control may result in death

USA. The US FDA has received reports of death and life-threatening changes in breathing and heart rate in patients taking methadone. These events occurred in patients newly starting methadone for pain control and in patients who had switched to methadone after being treated

for pain with other strong narcotic pain relievers. The US FDA is warning users that methadone stays in the body for about 8 - 59 hours after it is taken, this being much longer than its analgesic effect of about 4 to 8 hours. Patients may thus take an additional dose before the drug is adequately washed out of the body. This could lead to toxic build up of methadone in the body, with life-threatening effects on breathing and heart beat. Health professionals are advised to read and carefully follow the methadone prescribing information while patients are warned not to take more than the prescribed dose of methadone.

Reference:

Public Health Advisory. U.S. Food and Drug Administration, 27 November 2006 (www.fda.gov).

Non-selective non-steroidal anti-inflammatory drugs (NSAIDs)

Review completed; overall benefit-risk favourable

Europe. The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) has concluded that the benefit-risk balance for non-selective NSAIDs remains favourable. This conclusion was based on a review announced in September 2006 of new thrombotic cardiovascular safety data. An EMA Press Release states that non-selective NSAIDs:

- are important treatments for arthritis and other painful conditions;
- may be associated with a small increase in the absolute risk for thrombotic events, especially when used at high doses for long-term treatment;

- have an overall favourable benefit-risk balance when used in accordance with the product information and taking into account the patient's individual risk factors (e.g. gastrointestinal, cardiovascular and renal).

The CHMP has reiterated its previous advice for doctors and patients to use the lowest effective dose for the shortest possible duration to control symptoms.

Reference:

Press Release (EMA/413136/2006). European Medicines Agency (EMA), 24 October 2006 (www.emea.europa.eu).

Terbinafine

Serious adverse effects including Stevens-Johnson syndrome

New Zealand. A *Prescriber Update* article reminds prescribers that serious adverse effects (AEs) such as liver failure, Stevens-Johnson syndrome and agranulocytosis can be caused by the use of oral terbinafine (Terbafin; Lamisil; Apo-Terbinafine). Case reports received by CARM in the last five years included nine terbinafine associated reactions that resulted in hospital admissions; another two were life-threatening, one with neutropenia with ulcerative stomatitis and elevated hepatic enzymes and another with agranulocytosis. Hepatitis (2 cases), pustular skin eruption (2), dermatitis exfoliativa (3), neutropenia (2) and agranulocytosis (1) were some of the other serious adverse reactions reported. Nearly all of the adverse reactions occurred within two months of terbinafine initiation. The article advises that oral terbinafine is not recommended in patients with active or chronic liver disease, and that patients should be asked to report symptoms suggestive of

blood dyscrasias or impaired liver function.

(Reports in the WHO database: Hepatic failure - 28; Stevens-Johnson syndrome - 69; Agranulocytosis - 49).

Reference:

Prescriber Update,
Vol 27(2): 19, 2006
(www.medsafe.gov.nz).

Tramadol-warfarin

Reports of interaction

New Zealand. According to a Medsafe *Prescriber Update* article there is sufficient evidence of an interaction between oral tramadol and warfarin, resulting in an elevated international normalized ratio (INR) and in some cases haemorrhage or bruising; but the mechanism is yet to be determined. According to the article, as on 31 July 2006 the CARM had received 116 reports of suspected adverse reactions to tramadol. Of these, three reports were of increased INR, ranging from 7.0 to 12.3, which occurred when oral tramadol was given to warfarin recipients. The onset time after tramadol initiation was one, two and seven days. A fourth warfarin recipient was also found to have haematoma and bruising eight days after tramadol initiation. The author, Dr Ruth Savage writes that it is unclear to what extent tramadol contributed to the elevated INR in the four cases because three patients were also receiving antibacterials, and the fourth patient may have taken an incorrect warfarin dose; but, in two of the cases, tramadol appeared to be the most likely cause. Dr Savage advises that close monitoring of INR should be undertaken when it is necessary to prescribe tramadol for warfarin recipients, particularly during the first week of tramadol treatment.

Reference:

Prescriber Update,
Vol 27(2): 23, November 2006
(www.medsafe.gov.nz).

The US FDA has formed a partnership with Duke Clinical Research Institute (DCRI) to develop tools to identify possible adverse effects that drugs and devices could have on the heart. A virtual electronic database of more than 200 000 electrocardiograms (ECGs), accumulated by the FDA from submitted clinical trial data, will be used to conduct the research. The FDA and DCRI are developing a consortium with various groups, organizations and the industry to coordinate and support an array of research projects that involve ECGs from clinical trials, and, through the consortium, gaps in cardiac biomarkers will be identified and projects will be prioritized according to those needs. The development of the ECG warehouse, digital ECG data standards and this partnership will enable biological measures to be identified and this will help 'predict which patients are at an increased risk for cardiovascular side effects'.

Reference:

FDA News. U.S. Food and Drug Administration,
27 September 2006
(www.fda.gov).

Swissmedic and Health Canada have signed a Memorandum of Understanding, for the exchange of information on therapeutic products (research developments, pharmacovigilance, electronic submissions and authorization of new medicines etc). Swissmedic has similar agreements with other regulatory agencies (US FDA, Australia's TGA).

The Swissmedic Press Release (in French) can be accessed at the following link:

www.edi.admin.ch/dokumentation/

Twenty-ninth Annual Meeting of Representatives of the National Centres Participating in the WHO Programme for International Drug Monitoring Liège, Belgium, 9-11 October 2006

Recommendations from working groups

1. Evidence of the need for pharmacovigilance: developing a simple standardized protocol

Sufficient data exist on the impact of adverse reactions to medicines. However, only a few studies have systematically compiled these data, particularly in the developing countries. Gathering evidence on adverse reactions to medicines and their socioeconomic implications would be an important first step in capturing support for pharmacovigilance in national medicines policies. The current working group exercise was undertaken to establish a standardized protocol that pharmacovigilance centres could use to collate and compile national data on the impact of adverse reactions to medicines.

The working group focused on two aspects: (1) type of data to collect and (2) sources of such data.

(1) The data to collect should be adverse reactions to medicines resulting in hospital admissions; fatalities; disabilities; prolonging hospital stay; number of working days lost to adverse reactions to medicines; expenses incurred in treating adverse reactions to medicines, effects on special patient groups and the impact of traditional medicines.

(2) Sources of data for the above could come from hospital admissions and discharge records, pharmacy dispensing records, treatment registers (hospitals, prescribers, private clinics), pregnancy registers, ambulatory care registers, health insurance claim records, medical records, public health programmes and toxicology centres. The data can be collected either retrospectively or prospectively depending upon available facilities and the infrastructure of the country.

Recommendations: It was suggested that all national pharmacovigilance centres should identify the incidence and impact of adverse reactions to medicines. For this purpose, studies should be conducted at the national level. Observational studies on specific adverse reactions to medicines might be carried out. The information from such studies would highlight medicine safety issues and influence medicines policies. A draft protocol for such studies should be developed and submitted to the WHO Advisory Committee on the Safety of Medicinal Products for a full review. The reviewed protocol could then be implemented in some countries as a pilot.

2. Types of monitoring required when new medicines are introduced in resource-limited countries

The procedures available for monitoring the safety of medicines were reported. Spontaneous reporting was used in all countries present. Other methods used were observational studies on specific adverse reactions to medicines when needed; active surveillance on targeted practitioners during the first twelve months; conditional approval for a period of two years with hospital monitoring in case of limited distribution of a medicine; intensive hospital monitoring for five years and after five years for serious adverse reactions to medicines; prescription event monitoring for five years; and a computerized register system for hospitals .

Recommendations: When the medicine is well known and its safety profile is good, spontaneous reporting is sufficient. In the other situations, mandatory reporting is required. It is the responsibility of the Marketing Authorization Holder to prepare a risk management plan for the new medicines and to undertake intensive monitoring for these products. National authorities should assess the adverse reactions to medicines , review the protocols and conduct epidemiological studies (cohort, clinical trials etc).

3. Types of monitoring required when new medicines are introduced in developed countries

The working group noted the challenges in modernizing pharmacovigilance systems in developed countries. It was noted that there is a need for additional tools in developed countries since routine spontaneous reporting is generally not sufficient for addressing all safety issues and evaluating the Periodic Safety Update Reports (PSURs) is not the solution for this problem. Challenges discussed during this working group were which medicines need more monitoring, what are the methods that could be used for this purpose, how to link pre-approval to post-approval observations, who should be responsible for this monitoring and who should fund these activities.

Recommendations: No recommendations could be made since all the methods were expensive and imposed varying degrees of burden on health-care professionals. The challenges remain. It is important to monitor also herbal medicines which are newly introduced into the market. Particular attention should be given to herbal medicines reporting because of their interaction with conventional medicines which may lead to adverse reactions to medicines.

4. Safety monitoring for pandemic flu-vaccines and emergency situations

During this workshop, there were four presentations on pharmacovigilance plans in Canada, the European Union (EU) and at the global level in the event of a pandemic flu. Special needs for post-marketing surveillance in emergencies, including issues such as data collection and analysis, information sharing/communication and decision making were highlighted.

In Canada the seasonal programme for flu vaccination currently administers 11 million vaccine doses per year, primarily to defined target groups. To prepare for post-marketing surveillance in a pandemic flu situation, several pilot projects during the annual flu vaccination are planned or ongoing. These include extended vaccine safety (including active follow-up of 1000 persons) and immunogenicity studies; timely electronic submission of adverse event reports; a web-based vaccine safety alert network; an expert consultant network for conducting standard investigation protocols for selected severe adverse events, and "real-time" causality review by an expert committee.

In the EU, draft Pharmacovigilance Plans for Pandemic Influenza Vaccines have been developed in collaboration with several stakeholders to be applied by all vaccine manufacturers when a pandemic is declared. It is based on routine pharmacovigilance activities (spontaneous reporting, PSURs, signal detection) and additional post-authorization safety studies when needed.

In discussing the global needs for vaccine pharmacovigilance in emergency situations, it was noted that a critical factor is whether the vaccine is in routine use with information on the safety profile already available, or a novel vaccine (such as a pandemic flu vaccine) with its safety profile in a general population largely unknown. Pharmacovigilance for pandemic flu vaccines should enable health authorities and governments to make robust decisions during the pandemic, and enable international collaboration and sharing of data. Safety data should be made available to WHO in order to feed into the global influenza programme. The *WHO Guidelines on Regulatory Preparedness For Human Pandemic Influenza Vaccines* addresses implementation of post-marketing surveillance for vaccine safety and effectiveness; surveillance in different target groups; benefit-risk assessment; responsibilities of stakeholders, and communication needs.

The group discussed some of the uncertainties with pandemic flu vaccination and factors that are likely to differ between countries and the challenges these might present for pharmacovigilance. They include the availability of vaccines, the pandemic influenza attack rate, vaccination strategies (including type of vaccine and vaccination settings) and prioritization of target populations by countries, health-care systems, data sources and types of surveillance, potential widespread systemic disruptions, and whether experience with seasonal flu vaccine would be generalizable or not.

Overall, the group agreed that adverse event reporting would have to be subject to minimal disruption during a pandemic; simple reporting forms with a minimum set of data fields, standard case definitions and timely electronic submission are desirable. Annual influenza campaigns can be used to test out surveillance plans, to expand capacities and improve efficiencies in countries, and to improve signal detection and global communication capacity.

5. Global networking

The issue of information sharing among drug regulators (or pharmacovigilance centres) has been addressed many times, but, non-public information or pre-decisional information is rarely shared in reality. The main information that is important to share concerns drug withdrawals since the media often report ahead of health professionals who are kept in the dark and new safety precautions for drugs. There are several important initiatives in place between regulators for sharing information but these require confidentiality agreements to be in place. It was noted that Vigimed (a confidential electronic discussion group for pharmacovigilance issues organized by the Uppsala Monitoring Centre, UMC, Sweden) would be a very useful platform to share this kind of news, but is currently under-utilized and the contents and procedures need to be redefined. The challenges for sharing this information are bureaucracy and the issue of confidentiality and liability.

Recommendations: WHO should explore the possibility of having a confidential web site where all regulators could post information; this should be discussed at the next International Conference of Drug Regulatory Authorities (ICDRA). Vigimed should be enhanced including discussion of different subjects, becoming more interactive, and have access to more information resources; funds should be identified for a full-time facilitator. WHO should follow up alert systems from major regulatory authorities and then utilize Vigimed as the platform to communicate. National Pharmacovigilance Centre twinning arrangements among emerging countries and developed country members should be encouraged. The UMC signal reviewer's panel could be used as a technical resource for National Pharmacovigilance Centres' concerns. This issue should be followed up at the next annual meeting.

6. Reviewing and evaluating PSURs

This working group discussed the difficulties perceived by Competent Authorities (CA) in terms of PSURs, the amount of data collected from PSURs, presentation and quality of this data and resources allocated for evaluation of PSURs. The usefulness of PSURs for signal detection, how to obtain reliable data on patient exposure, the lack of epidemiological data on baseline incidence of disease and comparison of data within a class of drugs were also perceived as difficulties.

Recommendations: Sharing of the workload between regulators may be of value. This has proved positive within the EU and may be extended to nationally registered drugs. The use of PSURs for drugs already marketed in other parts of the world for registration may be useful. Expertise is needed for assessment. PSURs could be developed in order that they might become Annual Safety Update Reports. PSURs should be simplified, should also include clinical trial data and post-marketing surveillance, and be evaluated by different partners. Because of dissimilarity on data available in the EU and USA, it would be worthwhile to exchange experience between the US FDA and the European Medicines Agency (EMA) in terms of PSURs.

7. Collaborating with vaccine programmes to improve monitoring of adverse events following immunization (AEFI)

This working group discussed specific key recommendations from the WHO consultation on global monitoring of AEFI, focusing on the most relevant to national centres and identified actions to move the recommendations forward.

The working group participants represented the existing complexity and different models in AEFI monitoring; among the twelve countries represented there were five different patterns of AEFI/ADR reporting to the national level and to the UMC. The group acknowledged that to address the recommendation of improving reporting to the UMC a more complete picture is needed in order to know how to engage the immunization community more broadly. Participants emphasized the fact that reporting AEFI is the best way to counter fears regarding vaccine safety, especially those expressed by anti-vaccination groups.

Further work is needed to explore the determinants of AEFI reporting and address them with specific strategies. In some countries there remains a reluctance by immunization programmes to focus on AEFI, however, positive examples were shared of concerted and successful efforts to engage the immunization community to improve reporting in some countries. The group noted that sharing country-specific experiences on a broader basis is extremely informative and a forum is required. The use of Vigiflow (a tool for the online reporting of adverse reactions to medicines) for AEFI reporting was discussed with pros and cons expressed by members of the group. In order to address the recommendation arising from the WHO consultation to improve resources and methods for reporting and analysis of vaccine adverse events data, the utility of Vigiflow (and other UMC tools) is to be further assessed by WHO in collaboration with the UMC and modified where possible. Different options for using a vaccine specific discussion group analogous to Vigimed were discussed. Issues considered included whether Vigimed should serve primarily for sharing information or have a separate focus for vaccines. For example, it was felt that there is a need to have different discussion groups developed for different areas of interest such as clinical case discussions.

With respect to harmonizing terminologies, the group heard a presentation on the Brighton Collaboration and participants were encouraged to contribute to the work of the Collaboration (contact: secretariat@brightoncollaboration.org). It was noted that standardized case definitions developed by the Brighton Collaboration could have relevance for pharmacovigilance in general. There was strong support for advocacy documents specific to vaccines to be developed to facilitate the collaboration between vaccines programmes and National Pharmacovigilance Centres to improve AEFI monitoring.

8. Patient safety monitoring project

The patient safety pilot project and its objectives were described briefly. A training video film of an error in administering intrathecal vincristine which highlighted multiple system errors was shown. A study on the assessment of preventability of adverse reactions to medicines was presented which showed that the percentage of preventable adverse reactions to medicines leading to hospital admission was 8.2%. Medication errors associated with preventable adverse reactions to medicines and related to medication use system occurred most often at the stages of administration and prescribing.

In order to obtain more information on medication errors, the participants suggested that national centres should conduct studies:

- to collect and identify reports with significant medication errors
- to establish consensus on the reports to identify the most significant situations

- to perform a root-cause analysis for observed errors
- to analyse new signals of medication errors
- to identify situations, occurrences, incidences, etc. that are most prone to errors and establish preventive programmes.

The protocol of the study might be retrospective or prospective. The analysis of data will need terminology and methods adapted to the new concept of patient safety, in order to detect signals and there by put into place preventive strategies. As with adverse reactions to medicines, medication errors will be submitted to the UMC by methods commonly used by the different countries.

Recommendations: A classification and taxonomy of medication errors is needed to allow national pharmacovigilance centres to participate in the Patient Safety project.

"Developing Pharmacy Practice - a Focus on Patient Care", a Handbook by the International Pharmaceutical Federation (FIP) and WHO

The overarching message of this handbook is that there is an important and rewarding professional role for pharmacists beyond pharmaceutical product supply and management. The handbook defines good pharmacy practice and presents a step-wise approach to pharmaceutical care within a general practice environment anywhere in the world.

The handbook is written for pharmacists, educators and students everywhere and in all health-care settings. Founded on the principles of the 'seven-star pharmacist', this interactive handbook provides practical examples and care models towards self-teaching. A wide variety of illustrative case studies are provided to meet the needs of different users. The book is designed to guide learners towards specific educational outcomes, and enable them to undertake tasks which require a combination of knowledge, skills and attitudes.

Part 1 considers some definitions of good pharmacy practice in different contexts.

Part 2 presents a step-wise approach to pharmaceutical care, within a general practice environment. It also stresses the value of appropriate referral in overall patient care. It looks at the need to assimilate and manage information and new developments, some trends in evidence-based practice, and the use of guidelines to inform medicine selection within specific contexts. The importance of patient beliefs, preferences, knowledge, rights and choices is also emphasized.

A CD-ROM is enclosed in the handbook and contains the majority of reference documents cited in Parts 1 and 2. The handbook is in English; a French version will soon be available in both electronic and print formats.

This new publication can be downloaded from the WHO Medicines home page (www.who.int/medicines), under Latest Publications.



World Health
Organization

The International Pharmacopoeia Fourth Edition

This new edition consolidates the texts of the five separate volumes of the third edition. In preparing this consolidated edition the opportunity has been taken to review the General notices of the *Pharmacopoeia*. Certain additions and amendments have been made to the notices in order to clarify the interpretation of the *Pharmacopoeia* and to facilitate application of the requirements by the user.

The opportunity has also been taken to improve certain aspects of the layout and format of the publication. In this Fourth edition all the monograph texts are brought together in one section and the method texts in another. Each of these major sections are divided into appropriate sub-sections and the method texts are numbered for ease of cross-reference.

New monographs for the following antiretroviral substances are published in the Fourth edition: didanosine, indinavir sulfate, nelfinavir mesilate, nevirapine, zalcitabine, zalcitabine mesilate, zalcitabine mesilate, and zalcitabine mesilate.

Revision of the current monograph for Oral rehydration salts has been carried out to conform to the modified formula published in the *13th Model List of Essential Medicines* (WHO Technical Report Series, No. 920, 2003) and in the *WHO Model Formulary 2004*. The revised formula has a reduced sodium chloride and glucose content providing a solution with a reduced osmolarity of 245 mOsm/l. Due to the improved effectiveness of the reduced osmolarity ORS solution, especially for children with acute, non-cholera diarrhoea, WHO and UNICEF now recommend that countries use and manufacture this formulation in place of the previously recommended ORS, i.e. the one published in the third edition of *The International Pharmacopoeia*, which has a total osmolarity of 311 mOsm/l.

Method texts that have been updated include, for example, the text on high performance liquid chromatography (HPLC). This has been revised to clarify certain technical terms and to add advice on adjustment of chromatographic conditions, as recommended by the *WHO Expert Committee on Specifications for Pharmaceutical Preparations* in October 2004.

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The International Pharmacopoeia, 4th edition

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