

No. 2, 2002

EDITORIAL

In addition to the regular articles on regulatory decisions and safety issues, in this edition, you will find a small item on the use of praziquantel. This describes an important advance in the treatment of schistosomiasis for pregnant women and women of child-bearing age with the recommendation that praziquantel can be used in these populations provided adequate monitoring takes place. This is a major challenge to pharmacovigilance programmes wherever schistosomiasis is endemic.

In the last issue of the newsletter we published an article on the use of metamizole sodium in Brazil. Some of our readers have expressed reservations about the article. We reiterate that the article on metamizole does not, in any way, reflect WHO's position on the drug. The intention was to open a debate on the need for continued monitoring of older generic drugs and to remind our readers of the necessity always to compare safety with similar products on the market. We now invite specific comments to the article and would be pleased to publish those and other concerns in the next issue of our newsletter.

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- Regulatory matters**
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We also wish to bring to your attention the upcoming events: the Annual Meeting of National Centres in Amsterdam and the Regional training course on pharmacovigilance in Canberra. We hope to see many of you at one of these events.

Lastly, we are holding a one-day workshop on "The Impact of Regulation on the Safe use of Drugs". This will be held immediately prior to the International Conference of Drug Regulatory Authorities (ICDRA) in Hong Kong in June 2002. A full report of this will be published in the next edition of this newsletter.

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ACARBOSE

Revised precautions for Acarbose and others

Japan. Korosho Japan has ruled that the package inserts for acarbose, zafirlukast and vincristine sulfate should be appropriately revised to reflect the serious adverse drug reactions (ADRs) being reported with these drugs. The precautions section in the package insert for acarbose (Glucobay) will now include the statement that acarbose can cause serious hepatic function disorders such as fulminant hepatitis. Hepatic function tests are advised once a month during the first six months after starting treatment with the drug and at longer but regular intervals thereafter. Hepatic function disorders and jaundice are to be added as serious ADRs in the package insert for zafirlukast (Accolate) while 'bone marrow depression' and 'interstitial pneumonia' will be in the precautions section for vincristine sulfate (Oncovin).

Reference:

Pharma Japan No. 1785: 11, 4 Mar 2002.

CYPROTERONE WITH ETHINYL-ESTRADIOL

Risk of venous thromboembolism

New Zealand. Cyproterone-containing estrogen pills (Diane-35/35D, Estelle-35/35D) are used to treat conditions caused by an excess of the hormone androgen, e.g. pronounced acne. These pills provide oral contraception as well. In a letter to doctors, midwives and pharmacists, the Medicines Adverse Reactions Committee (MARC) for New Zealand has advised that the risk of venous thromboembolism (VTE) with oral contraceptives (OCs) containing cyproterone acetate and ethinylestradiol is at least as

great as that with third generation OCs. The Centre for Adverse Reactions Monitoring in Dunedin, New Zealand has received 18 reports of VTE, including 15 of pulmonary embolism, in women taking cyproterone-ethinylestradiol pills. MARC reminds practitioners that cyproterone-ethinylestradiol combination pills are indicated only in women for the treatment of androgen-dependent diseases (including pronounced acne) and polycystic ovary syndrome and for oral contraception in these women. All patients currently on these medicines should be reviewed at their next visit (or repeat prescription) for the appropriateness of this therapy. Both new and current patients should be fully advised of the risks of VTE and be informed of the symptoms of VTE and situations of increased risk. The advice from MARC is based on a study in the Lancet (2002) and other previously published smaller studies. Medsafe has also updated the June 2000 patient leaflet on OCs and blood clots to include the above information.

Reference:

1. *Prescriber Update Article – Letter to Doctors/Midwives/Pharmacists about VTE with cyproterone-containing OCs, Mar 2002.* Available from URL: <http://www.medsafe.gov.nz>
2. *Medsafe Patient Information Leaflet on oral contraceptives and blood clots, Mar 2002.* Available from URL: <http://www.medsafe.gov.nz>
3. *Lancet 359: 1085-1101, 2002.*

ENOXAPARIN SODIUM

Important changes to injection product labelling

USA. FDA and Aventis Pharmaceuticals have strengthened the Warnings and Precautions sections of the prescribing information for enoxaparin sodium (Lovenox) injection. Healthcare professionals are informed that the use of this injection is not

recommended for thromboprophylaxis in patients with prosthetic heart valves. This warning follows reports of prosthetic heart valve thrombosis in patients who had received enoxaparin. Some of these patients were pregnant women in whom thrombosis led to maternal and foetal deaths. Pregnant women with prosthetic heart valves may be at higher risk for thromboembolism. A paragraph has been added to the 'teratogenic effects' subsection regarding reports of congenital anomalies including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defect in infants born to women who received enoxaparin during pregnancy. The non-teratogenic effects subsection has also been revised to indicate that pregnant women receiving anti-coagulants, including enoxaparin, are at increased risk for bleeding; hemorrhage can occur at any site and may lead to death of mother and/or foetus. Pregnant women and women of child-bearing potential should be apprised of the hazard to the foetus and the mother if enoxaparin is administered during pregnancy.

Reference:

'Dear Healthcare Professional' letter by Aventis Pharmaceuticals, Feb 2002. Available from URL: <http://www.fda.gov/medwatch/SAFETY/2002>

HERBAL DIETARY SUPPLEMENTS (PC-SPES & SPES)

Adulteration with prescription only medicines precipitates regulatory action

Canada, Ireland, USA. PC-SPES and SPES are herbal medicines manufactured by Botanic Lab in the USA. The two products are marketed as 'herbal

dietary supplements' for 'prostate health' and for 'strengthening the immune system' respectively. These are sold through the internet, by mail and phone order as well as through various distributors and healthcare professionals. An analytical report from the California Department of Health, USA showed that samples of PC-SPES and SPES were adulterated with warfarin and alprazolam respectively. The Canadian medicines regulatory authority has also reported similar contamination. Warfarin is an anticoagulant (blood-thinning agent) which can cause serious bleeding, particularly if taken with other medications without prior supervision while alprazolam is a prescription only medicine used in the treatment of anxiety. In view of these reports Health Canada, the Irish Medicines Board and the State Health Director of California, USA have all warned consumers to immediately stop using these two products and to consult their health-care practitioners. Botanic Lab has also informed consumers of these laboratory findings and has issued a product recall of all lots of PC SPES pending further reports from additional testing of PC SPES in both commercial as well as academic laboratories.

Reference:

1. *Warning from the Office of Public Affairs, California Department of Health Services, 7 Feb 2002.*
Available from URL:
<http://www.fda.gov/medwatch/SAFETY/2002>
2. *'Dear customer' letter from Botanic Lab, 8 Feb 2002.*
Available from URL:
<http://www.fda.gov/medwatch/SAFETY/2002>
3. *Health Canada Warnings/Advisories, 8 Feb 2002.*
Available from URL:
<http://www.hc-sc.gc.ca>
4. *Current News and IMB Statements, 15 Feb 2002.*
Available from URL:
<http://www.imb.ie/>

HUA FO

Sildenafil detected in tablets

Canada. Health Canada has analysed and detected the presence of sildenafil in Hua Fo Tablets, an unapproved herbal product that claims to enhance sexual function. Sildenafil is a prescription-only drug approved for the treatment of male erectile dysfunction. Health Canada is warning consumers not to use Hua Fo Tablets since the use of sildenafil without medical supervision could cause severe adverse reactions such as potentially life-threatening low blood pressure in the presence of concurrent treatment with other medications such as nitrates. Although to date no adverse reactions have been reported to Health Canada involving the use of Hua Fo, consumers who have used Hua Fo are nevertheless being advised to contact their physicians. Health Canada has issued this warning to advise consumers, healthcare professionals and the provincial ministries of health of the safety issues related to the use of Hua Fo. Hua Fo is manufactured in China by Guizhou Ribulo Medical Industry Inc. and sold in Canada by Shenlong Company. Health Canada is also working with the importer of the product to ensure its removal from the market.

Reference:

Health Canada Warnings/Advisories, 15 Feb 2002.
Available from URL:
<http://www.hc-sc.gc.ca>

INTERFERON ALFA 2B, RECOMBINANT

Safety related labelling change

USA. Schering Corporation, the manufacturer of interferon alfa 2b (Intron A) has issued a letter to health professionals informing them of safety related labelling changes to the product information for all alpha

interferons. The change includes the addition of a boxed warning stating that neuropsychiatric, autoimmune, ischemic and infectious disorders may be aggravated in patients taking interferon alfa 2b (Intron A). The revised warning also includes specific requirements for monitoring these patients for life-threatening adverse events. Patients with persistently severe or worsening signs or symptoms of the above mentioned conditions should be withdrawn from therapy. In many but not all cases these disorders are expected to resolve after stopping therapy.

Reference:

'Dear Health Professional' letter from Schering Corporation, 14 Mar 2002. Available from URL:
<http://www.fda.gov/medwatch/SAFETY/2002>

KAVA-KAVA

Further investigations into Piper methysticum and liver injury

New Zealand, Canada, Ireland, USA. Further to the precautionary warnings issued by the regulatory authorities in Germany, Switzerland, UK and USA (Pharmaceuticals Newsletter No. 1, 2002), the following actions have been recorded on the use of Kava.

16 January 2002: The New Zealand Ministry of Health has stated that it is looking into concerns expressed by overseas authorities about a reported link between kava consumption and liver damage in some people. In New Zealand Kava is mostly consumed as a natural drink whereas in Europe it is consumed as a pre-packaged dietary supplement. Since factors other than kava consumption may have caused liver damage, it is difficult to draw a definite cause-effect relationship with the present evidence in New Zealand. However the ministry has been working closely with the Australia New Zealand Food

Authority (ANZFA) since it became aware of this issue in early January to gather relevant information and is awaiting further information from Europe before reaching a conclusion on whether any action is warranted.

16 January 2002: Health Canada has advised consumers not to use any product that contains kava although no cases of liver toxicity have been reported in Canada with Kava. Health Canada is conducting a comprehensive safety assessment of kava and will take further action, if required, on completion.

4 February 2002: The Irish Medicines Board in consultation with the industry initiated a voluntary withdrawal of all products containing kava from the Irish market with immediate effect although the Medical Director at IMB stated that the current data are confounding. The IMB based its withdrawal on similar actions by other EU Member States.

25 March 2002: The US FDA is advising consumers of the potential of liver injury with the use of kava-containing dietary supplements. Persons who have liver disease or liver problems, or persons who are taking drug products that can affect the liver have been advised to consult a physician before using kava-containing supplements. Consumers who use kava-containing dietary supplements and who experience signs of illness associated with liver disease should also consult their physician. The FDA has also issued a letter to health-care professionals informing them of the consumer advisory and has urged consumers and their health-care professionals to report any cases of liver and other injuries that may be related to the use of kava. In the meanwhile the FDA will continue to investigate the relationship, if any, between the use of dietary supplements containing kava and liver injury.

Reference:

1. *Media Release, 16 Jan 2002.*
Available from URL:
<http://www.ndp.govt.nz/media>
2. *Health Canada Warnings / Advisories, 16 Jan 2002.*
Available from URL:
<http://www.hc-sc.gc.ca>
3. *Current News and IMB Statements, 4 Feb 2002.*
Available from URL:
<http://www.imb.ie/>
4. *Consumer Advisory, 25 Mar 2002.* Available from URL:
<http://www.cfsan.fda.gov/>
5. *'Dear Healthcare Professional' letter by US FDA, 25 Mar 2002.*
Available from URL:
<http://www.cfsan.fda.gov/>

NEFAZODONE

New black box warning to report rare cases of liver failure

USA. Due to reports of rare cases of nefazodone (Serzone)-associated liver failure leading to transplant and/or death, a black box warning has been added to the product information in the US, according to a 'Dear Healthcare Practitioner' letter posted on the FDA's website. The warning is based on the postmarketing experience of >7.2 million US patients, and includes the following information.

- The reported rate of liver failure associated with nefazodone is approximately 1 case per 250,000-300,000 patient-years.*
- Nefazodone is not recommended for use in patients with acute liver disease or elevated baseline aminotransferase levels, which can complicate patient monitoring.
- Patients should be advised to be vigilant for symptoms or signs of liver dysfunction, and to seek advice from their physician should any become apparent.
- Nefazodone should be withdrawn in patients who exhibit signs or symptoms of liver failure, or if evidence of hepatocellular injury develops. Furthermore, such

patients should be assumed to be at increased risk of developing liver injury if nefazodone is restarted, and therefore this should not be considered.

Additional information is included in the appropriate sections of the labelling for nefazodone.

* 3-4 times greater than the estimated background rate

Reference:

'Dear Healthcare Practitioner' letter from Bristol-Myers Squibb, 9 Jan 2002.
Available from URL:
<http://www.fda.gov>

ORAL CONTRACEPTIVES

Risk of cervical cancer with long-term use in women with high risk type of HPV

UK. The Chief Medical Officer from the UK Department of Health has issued an urgent communication to all Health Professionals with the following information: A recent study published in the *Lancet* (2002), although not conclusive, strengthens the evidence that oral contraceptives (OCs) may contribute to the development of cervical cancer in women with high risk type human papilloma virus (HPV). The study reports an association between increasing risk of cervical cancer and increasing duration of use of OCs (3 fold increase in risk following 5-9 years of OC use versus 4-fold increase after 10 or more years of OC use) in women with HPV. HPV is a sexually transmitted infection. There are more than 80 HPV viruses, only a few of which are associated with an increased risk of cervical cancer. With the current evidence it is difficult to state whether it is the use of OCs, sexual activity, the type of HPV or the duration of HPV infection which is/are the main precipitating factor(s) for cervical cancer. Furthermore, the original

studies were carried out in women from developing countries with no adequate cervical screening programme. While cervical screening is not perfect, between 80% and 90% of cervical abnormalities can be detected and treated in women who attend regular screening programmes. The communication therefore advises that all sexually active women, especially those on long-term OCs, be encouraged to have regular cervical smears. The benefits of using OCs outweigh the risks in the vast majority of women who use them.

Reference:

1. Urgent Communication from Chief Medical Officer, 27 March 2002. Available from URL: <http://www.mca.gov.uk>
2. Lancet 359: 1085-1101, 2002.

PAROXETINE
Withdrawal symptoms can be severe

USA. The US FDA published a new product warning for paroxetine regarding the severe withdrawal symptoms of the kind that could lead to dependence. Withdrawal symptoms such as bad dreams, paraesthesia and dizziness can occur in up to 7% of patients. The warning mentions anecdotal reports of agitation, sweating and nausea and tells doctors to consider restarting treatment if symptoms become intolerable. Welcoming the FDA safety warning Dr Peter Haddad, consultant psychiatrist for Salford's Mental Health Service NHS Trust has stated that there is a danger of misdiagnosis and inappropriate investigation of the symptoms following paroxetine withdrawal. For example, severe dizziness can easily be diagnosed for labyrinthitis. Patients should be warned not to stop taking their antidepressants suddenly; doctors should taper the dose at the end of treatment, keeping a close watch for withdrawal symptoms.

Reference:

British Medical Journal 324: 260, 2 Feb 2002.
Available from URL: <http://bmj.com>

SODIUM PHOSPHATES ORAL SOLUTION
Risk of electrolyte shift if maximum dose is exceeded

Canada. Sodium Phosphates Oral Solution has been marketed in Canada since 1987 as a laxative for the relief of occasional constipation. The product is also used as part of a bowel-cleansing regimen in preparing patients for surgery or for colonoscopy, etc. From 1987 up to October 31, 2001 the Canadian Adverse Drug Reaction Monitoring Program had received 10 domestic reports of serious electrolyte disturbances (hypocalcaemia, hyperphosphatemia, hypernatremia, hypokalemia and acidosis), dehydration, renal failure and tetany in patients ingesting more than 45 ml of the solution, in patients at medical risk and/or in patients using multiple purgatives for bowel preparation. In view of these reports, Johnson & Johnson o Merck Consumer Pharmaceuticals and Pharmascience Inc., in consultation with Health Canada have each issued a letter to all health professionals with information related to the safe use of sodium phosphates oral solution. The identification, characterization and management of drug-related adverse events is dependent on the active participation of health care professionals in adverse drug reaction reporting programmes. Healthcare professionals are requested to report any suspected adverse reactions in patients receiving sodium phosphates oral solution directly to Johnson & Johnson o Merck Consumer Pharmaceuticals (Fleet® Phospho-Soda®) or to Pharmascience Inc.

Reference:

1. 'Dear Healthcare Professional' letter by Johnson & Johnson o Merck Consumer Pharmaceuticals, Canada, 15 Mar 2002. Available from URL: <http://www.hc-sc.gc.ca>
2. 'Dear Healthcare Professional' letter by Pharmascience Inc. Canada, 18 Mar 2002. Available from URL: <http://www.hc-sc.gc.ca>

TAMOXIFEN
Prevention in breast cancer versus risks of thromboembolic events

UK. Tamoxifen is already a widely used hormonal treatment for women following treatment for early and advanced breast cancer. Now, in addition to its use as a treatment in cancer, preliminary results from the International Breast Cancer Intervention Study (IBIS) provide evidence also for the use of tamoxifen to 'prevent' breast cancer in healthy women at high risk. The results so far show that the incidence of breast cancer was reduced by one-third in women at high risk, compared to women taking a placebo. The study also indicated, however, that tamoxifen can increase the risk of thromboembolism, particularly during and immediately after major surgery or periods of immobility. The UK Department of Health has sent out an urgent communication with the above information to all directors of public health. The key messages in the communication may be summarised as under:

1. It is clear that the benefits for women being treated for breast cancer with tamoxifen far outweigh the risks. It is important that women taking the drug as a treatment continue to do so as there is overwhelming evidence that tamoxifen saves life among women with breast cancer. There is evidence of some increase in risk from thromboembolism with tamoxifen, especially during and immediately after major surgery or periods of immobility. Patients

should be made aware of the symptoms of venous thromboembolism and if they have any sudden onset of breathlessness they should consult their doctor immediately.

2. The IBIS study gives evidence of the preventative action of tamoxifen in breast cancer. However this is not a use of tamoxifen that has yet been licensed except in the context of a trial.

3. A full analysis of all trials needs to be carried out to consider whether the benefits of preventative action outweigh potential risks.

Reference:

Urgent Communication from Chief Medical Officer, 27 Mar 2002.

Available from URL:

<http://www.mca.gov.uk>

ZIPRASIDONE HCl

Warnings and contraindications sections strengthened

USA. The US FDA and Pfizer have strengthened the Warnings and Contraindications sections of the ziprasidone (Geodon) prescribing information to inform healthcare professionals of the particular drugs or types of drugs that are contraindicated with ziprasidone. The revisions are being made only to clarify existing information in the package insert. The earlier contraindications section included a list of seven drugs contraindicated with ziprasidone and stated that this list of drugs was 'not a complete list'. Not all physicians, pharmacists and pharmacy databases interpreted this language as intended. Some may have considered certain drugs excluded from the contraindication while others may have believed that, irrespective of the level of documentation, any drug associated with QT-prolongation was contraindicated with ziprasidone. Pfizer and FDA

agreed that there was a need to provide greater clarity around the particular drugs or types of drugs that are contraindicated with ziprasidone. The key sections that have been changed in the label now clearly state that an additive effect of ziprasidone and other drugs that prolong the QT interval cannot be excluded. Therefore, ziprasidone should not be given with dofetilide, sotalol, quinidine, other class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozone, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. Ziprasidone should be avoided in combination with other drugs that are known to prolong QTc interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QTc interval. Such drugs should not be prescribed with ziprasidone. Ziprasidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Reference:

Letter from Pfizer, Mar 2002.

Available from URL:

<http://www.fda.gov/medwatch/SAFETY/2002>

ALENDRONATE

Case reports of pancreatitis with alendronic acid suggest a link?

Canada. Six case reports of pancreatitis associated with alendronic acid therapy have been received by the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) between the time the agent was launched in Canada (December 1995) and August 2001, according to an article in the Canadian Adverse Drug Reaction Newsletter. The article notes that, based on these cases, it is difficult to establish a causal relationship between alendronic acid and pancreatitis, as the case reports contain limited data. However, in one of the case reports, the patient had been receiving alendronic acid monotherapy for 13 days when pancreatitis developed, and the complication resolved after she discontinued the drug. Furthermore, that patient did not have any additional risk factors for pancreatitis. In the remaining case reports, the onset of symptoms of pancreatitis after initiation of alendronic acid therapy ranged from 48 days to several years (data not provided for 2 patients), and the patients were elderly and female where such data were provided. One woman died, and her death was reported to be possibly drug related. The article calls for the continued reporting of other suspected cases of alendronic acid-associated pancreatitis, to assist in further assessment of this possible adverse drug reaction.

Reports in WHO-file: Pancreatitis 48

Reference:

Canadian Adverse Drug Reaction Newsletter 12(1): 2-3, Jan 2002.

AMIODARONE

Reports of pulmonary toxicity

Australia. Since 1981, Adverse Drug Reactions Advisory

Committee (ADRAC) has received 31 reports of fatal adverse events associated with amiodarone use. 17 of these involved pulmonary events, including pulmonary fibrosis (8 reports) and pulmonary infiltration (5). The committee warns that pulmonary toxicity associated with amiodarone use can develop rapidly. It suggests that amiodarone be used at the lowest effective dose, and that the development of dyspnoea or non-productive cough in patients receiving amiodarone should be investigated immediately.

Reference:

Australian Adverse Drug Reactions Bulletin 21: 2, Feb 2002.

ANTIRETROVIRAL THERAPY (ART)

Lipodystrophy syndrome with ART under-reported in Canada

Canada. Antiretroviral therapy (ART)-related lipodystrophy syndrome is 'highly under-reported' in Canada, according to a report in the Canadian Adverse Drug Reaction Newsletter. In the article, a working case definition of lipodystrophy syndrome is described as one with at least 1 metabolic abnormality and at least 1 clinical feature, in addition to no AIDS-defining event or other serious condition, or the use of anabolic steroids, glucocorticoids or immune modulating agents within the 3 months before assessment. Using this definition, 4 case reports of ART-associated lipodystrophy syndrome were identified from the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database. These case reports came from a total of 119 reports of metabolic, nutritional or endocrine disorders associated with antiretroviral agents. In addition, there were 3 cases of potential lipodystrophy syndrome and 13 cases of fat disorder. Of

the 4 cases of ART-associated lipodystrophy syndrome that met the working definition, 3 were associated with the protease inhibitors indinavir, saquinavir and zidovudine, and the remaining report was associated with stavudine. The patients included 3 men and 1 woman, and were aged 33-56 years. The clinical features of lipodystrophy syndrome included lipodystrophy (2 patients), fat disorder (2) and enlarged abdomen (1), and metabolic abnormalities included hyperglycaemia (2), hypertriglyceridaemia (2) and diabetes mellitus (1). The article points out that the prevalence of lipodystrophy syndrome during highly-active antiretroviral therapy has been reported by retrospective studies to be between 17 and 84%. As the incidence of lipodystrophy syndrome is therefore clearly under-reported to Health Canada, the Therapeutic Products Directorate has implemented a project to promote the reporting of adverse drug reactions in patients with HIV infection.

Reference:

Canadian Adverse Drug Reaction Newsletter 12(1): 3 - 4, Jan 2002.

ARISTOLOCHIA

Safety update from Oman

Sultanate of Oman. The Directorate General of Pharmaceutical Affairs & Drug Control (DGPA&DC) in the Sultanate of Oman has made a decision to prohibit the import and marketing of any herbal product or traditional medicines containing aristolochic acid. The decision was made in light of information received by the directorate that aristolochic acid consumption has been associated with severe kidney toxicity and also the development of cancer of the urinary tract.

Reference:

Directorate General of Pharmaceutical Affairs & Drug Control Pharmaceutical Newsletter 9: 1, No. 3, 2001.

BUPROPION

Risk of seizure

UK. The UK Medicines Control Agency has issued a new safety update for bupropion (Zyban) reminding prescribers that this aid to smoking cessation is contraindicated in patients with current or previous seizure disorder⁽¹⁾. The agency warns that bupropion should not be prescribed to patients with current or previous bulimia or anorexia nervosa, a known CNS tumour, or those abruptly withdrawing from alcohol or benzodiazepines. Bupropion should be prescribed with caution to patients with other risk factors for seizure, including concomitant use of drugs known to lower the seizure threshold. In such patients, a lower dose of 150 mg/day should be considered. Up to January 2002, the agency had received 168 reports via the Yellow Card Scheme of seizures suspected to be associated with bupropion. Approximately half of the patients with seizures had a history of seizure or risk factors for seizure. More recently, in February 2002, following a referral by Germany, the EMEA (European Medicinal Products Evaluation Agency) initiated a community level review of the risk – benefit data for bupropion (amfebutamine). The review is likely to take six months to complete⁽²⁾.

Report in WHO-file: Convulsions 1082, convulsions grand mal 459

Reference:

1. Media Release, 14 Jan 2002. Available from: URL: <http://www.mca.gov.uk>
2. The Pharmaceutical Journal 268: 274, 2 Mar 2002.

CLOZAPINE

Clear association with myocarditis; revised labelling to indicate cardiovascular toxicity

Canada. In January 2002, Novartis Pharmaceuticals, Canada, manufacturer of

clozapine (Clozaril), in consultation with Health Canada had alerted health professionals to the risk of cardiovascular complications with clozapine therapy. This association was based on post-marketing surveillance data for clozapine from four countries that employ haematological monitoring of clozapine-treated patients. The data included: 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (August 2001); 30 reports of myocarditis with 8 fatalities in 24,108 UK patients; 30 reports of myocarditis with 1 fatality in 205, 493 US patients. These reports represent an incidence of 96.6, 16.3, 43.2 and 5.0 cases per 100, 000 patient years respectively. More recently, Novartis has revised and relocated the Boxed Warning for clozapine (Clozaril) to the beginning of the Prescribing Information section. The revised boxed warning advises health care providers of the association of myocarditis with clozapine therapy. In a letter from Novartis Pharmaceuticals

- Health professionals are advised to consider myocarditis in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs of symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. Tachycardia has been noted as a presenting sign in patients with myocarditis. Therefore, patients experiencing tachycardia during the first month of therapy should be closely monitored for other signs of myocarditis.
- Physicians are advised to promptly discontinue clozapine therapy upon suspicion of myocarditis and not to re-challenge patients with clozapine-induced myocarditis with further exposure to clozapine.

Reference:

1. 'Dear Healthcare Professional' letter from Novartis, 14 Jan 2002. Available for URL: <http://www.hc-sc.gc.ca>
2. 'Dear Healthcare Provider' letter from Novartis, Feb 2002. Available for URL: <http://www.hc-sc.gc.ca>

DROPERIDOL

Warnings of cardiovascular toxicity

Canada. Further to the safety warnings and labelling changes notified by Akorn Pharmaceuticals in consultation with the US FDA for droperidol (WHO Pharmaceuticals Newsletter No. 1, 2002), Health Canada's Therapeutic Products Directorate has issued a letter to health professionals advising of cardiovascular toxicity associated with injectable droperidol. The letter advises that worldwide, more than 60 cases of QT prolongation, serious arrhythmia (such as torsade de pointes) and sudden death have been reported in association with the use of injectable droperidol. In Canada, 8 cases with a fatal outcome have been reported in association with the use of injectable droperidol and concomitant administration of anaesthetics, muscle relaxants, narcotic analgesics and anxiolytics. The agency advises that injectable droperidol should only be used in a hospital setting, it should not be used concomitantly with other drugs that prolong the QT interval, and that use of the drug should be avoided in patients who may be at risk of developing a prolonged QT interval. The agency suggests that all patients undergo a 12-lead ECG in order to determine if a prolonged QT interval is present and that injectable droperidol should not be used if such an interval is present. In addition, ECG monitoring should be continued after treatment completion, as QT prolongation and arrhythmias have occurred up to 24 hours after droperidol administration. Health Canada says that it is continuously

monitoring the post-marketing safety data for injectable droperidol and that further information will be available when their assessment of the situation is complete.

Reference:

Letter issued by Therapeutics Products Directorate, Health Canada, 12 Feb 2002. Available from URL: <http://www.hc-sc.gc.ca>.

EPHEDRINE/ EPHEDRA

Products recalled following risk assessment

Canada. Health Canada has requested a market recall of some products that contain ephedrine or ephedra following the conclusions of a risk assessment study that certain products containing these agents can pose a serious health risk. The voluntary recall affects products that have been marketed without approval and include those which meet the following criteria.

- Products with a dose unit of >8mg of ephedrine, or labelling that recommends >8 mg/dose or >32 mg/day, and/or are labelled or implied for use of >7 days.
- Products that contain ephedrine or ephedra in combination with stimulants, such as caffeine, or other substances that could enhance the effects of ephedrine or ephedra.
- Products with labelling, or an implication for use, for appetite suppression, body-weight loss promotion and other stimulant effects.
- Fatality with caffeine/ephedrine combination

The recall follows an advisory issued in June last year by Health Canada, in which the Canadian public was advised to avoid products containing ephedra in combination with caffeine or other stimulants. This advisory was issued in response to 60 adverse events reported in Canada in association with such

products. Adverse events associated with ephedrine and ephedra include stroke, heart attacks, arrhythmias, seizures and psychotic disorders. Some fatalities due to such events have also been reported. Since the advisory was issued, a product containing large doses of ephedrine with caffeine has been implicated as a contributing factor in 1 fatality in Canada. Health Canada has advised the Canadian public that anybody using the affected ephedrine- or ephedra-containing products should discontinue their use and return the product to the point of sale. The authority has also issued letters to companies involved in the manufacture, distribution, importation, and resale of affected products, and plans to undertake a random market survey within 6 months to assess if the recall has been effective.

Reference:

Health Canada Warnings/Advisories, 9 Jan 2002. Available from URL: <http://www.hc-sc.gc.ca>

METHOTREXATE

Adverse reactions influence treatment and prescribing decisions

India. A variety of adverse reactions and drug interactions recently reported in association with methotrexate have prompted the revision of prescribing and treatment decisions, the Indian National Pharmacovigilance Centre has reported. Skin and soft tissue necrosis has been seen when methotrexate and radiotherapy have been administered concomitantly. Also, reports have indicated that methotrexate may augment the hepatotoxic effects of other drugs, and patients receiving such a regimen should be closely monitored for liver disorders. The report concludes that most adverse reactions with methotrexate are reversible if detected early, and intervention should involve methotrexate

discontinuation or dosage reduction, along with specific treatment of the adverse reaction.

Reference:

Newsletter of the Indian National Pharmacovigilance Centre 3(1): 3, Nov 2001.

OLANZAPINE

Cardiomyopathy: case report

Sweden. A middle-aged man developed dilated cardiomyopathy during treatment with olanzapine (patient age and therapeutic indication not stated). The man, who had experienced a significant increase in bodyweight over the previous 6 months, was admitted to hospital for investigation. In addition, he had experienced dyspnoea, oedema in his legs, weakness, ascites and a hacking cough. He had been taking olanzapine (Zyprexa) 5 mg/day for 18 months, and had discontinued treatment with the agent one month prior to admission. The man was treated with antibacterials for a low-grade fever and inflammation. An ultrasound investigation showed a dilated left ventricle, and subsequent tests revealed a greatly reduced ejection fraction of 10-15%. In addition, he had 'poor' blood gases and was dehydrated. Treatment with digoxin, ACE inhibitors, β -blockers and diuretics was initiated. Two weeks later, an ultrasound scan revealed a reduced heart size, and a myocardial biopsy 2 months later showed discrete fibrosis with inflammation or incorporation. The man's symptoms improved and treatment with digoxin was discontinued. In addition, his diuretic dose was reduced. One year after admission, his ejection fraction had increased to 35-40%.

Reports in WHO-file:

Cardiomyopathy 13

Reference:

Information of Medical Products Agency 12: 76-77, Dec 2001.

ROFECOXIB/ WARFARIN

Clinically significant interactions possible

Australia. Since late 2000, the Australian Adverse Reactions Advisory Committee (ADRAC) has received 8 reports of increased International Normalised Ratio (INR) in patients simultaneously using rofecoxib and warfarin. Of these, 2 reports described bleeding events (epistaxis and rectal haemorrhage) and 1 described anaemia. The committee recommends increased monitoring of INR in patients taking warfarin and concomitant rofecoxib.

Reference:

Australian Adverse Drug Reactions Bulletin 21(1): 3, Feb 2002.

ROSIGLITAZONE

Reminder about restrictions in use

Singapore. The Health Sciences Authority in Singapore has issued a reminder to all prescribers that rosiglitazone is not recommended for use in patients with New York Heart Association class III or IV heart failure or moderate-to-severe hepatic impairment. In addition, they say that rosiglitazone is not recommended for use in combination with insulin. The Singapore Pharmacovigilance Unit has received 4 reports of suspected adverse drug reactions associated with the use of rosiglitazone since its release in Singapore in June 2000. Two of the cases were of heart failure, 1 was of peripheral oedema and the other was of mildly elevated liver enzyme levels. The authority says that liver enzyme levels should be monitored before initiating, and during, therapy with rosiglitazone. It adds that if liver enzyme levels remain more than 3 times greater than the upper limit of normal, rosiglitazone should be discontinued.

Reference:

Adverse Drug Reaction News 3: 2-3, Dec 2001.

SIBUTRAMINE

Safety reviews on anti-obesity drug

Canada, Europe. Health Canada has launched a safety review of the prescription drug sibutramine (Meridia) in view of the accumulating adverse reaction reports with the drug in Canada and elsewhere in the world. Sibutramine was approved for sale in Canada in December 2000 as an obesity treatment to be used in combination with diet and exercise. Although no deaths have been reported, there have been reports of adverse reactions associated with the use of sibutramine in Canada from December 2000 to February 2002. These reports are consistent with adverse reactions of sibutramine which include cardiovascular reactions such as increased blood pressure, chest pain, stroke as well as disturbances of vision such as eye pain and eye haemorrhage. Health Canada is contacting and collaborating with regulatory agencies in other countries in reviewing the safety of sibutramine and will communicate the results to the public and take further action if required. The market authorisation for all drugs containing sibutramine has been suspended in Italy since March 6, 2002 following 50 adverse reaction reports including seven serious cases and two deaths. Arrhythmia and cardiac arrest were reported to be associated with the two deaths. Several other European countries such as France, Germany, England, the Netherlands, Denmark, Portugal, Sweden, Finland and Spain have issued statements informing the public of this market suspension in Italy. France, Germany and England are conducting additional reviews but have not withdrawn the drug.

Reference:

Health Canada Warnings/Advisories, 27 March 2002.

Available from URL:

<http://www.hc-sc.gc.ca>

SODIUM PICOSULFATE

Reports of severe electrolyte disturbances

Australia. The Australian Adverse Reactions Advisory Committee (ADRAC) has received 12 reports implicating sodium picosulfate (Picolax and Picoprep) in severe electrolyte disturbances, including convulsions (5 reports), syncope (1), unconsciousness (1) and metabolic alkalosis (1). An additional 4 reports described syncope and dehydration without electrolyte disturbance. ADRAC warns that low volume bowel preparations containing sodium picosulfate or sodium phosphate should be avoided in infants and the elderly as well as in those with congestive heart failure or compromised renal function.

Reference:

Australian Adverse Drug Reactions Bulletin 21(1): 2, Feb 2002.

STATINS

News from India and Singapore

India⁽¹⁾. The Indian National Pharmacovigilance Centre in its newsletter has presented details of 11 reports of hepatomegaly, and 6 cases of liver cirrhosis, associated with atorvastatin. These reports are included in the WHO Adverse Drug Reactions database. Among the 11 cases of hepatomegaly, the complication occurred on the same day that treatment was initiated in some cases, but did not occur for nearly 2.5 years in others. In 5 of the cases of hepatomegaly, a 'definite improvement' was seen after atorvastatin therapy was withdrawn. Five of 6 cases of atorvastatin-associated liver cirrhosis included in the WHO Adverse Drug Reactions

database occurred within 12 months of treatment initiation, while the remaining case developed after almost 2.5 years' treatment. Cessation of atorvastatin therapy resulted in a definite improvement in these cases. 29 cases of cholestatic hepatitis associated with pravastatin use have been reported and these occurred between 1-6 months after treatment initiation. In its report, the centre has also presented data from the WHO Adverse Drug Reactions database on cases of vision disorders associated with statins. An association between optic ischaemic neuropathy and atorvastatin has recently become apparent, with 4 cases of this complication, blurred vision and visual field defects being reported, causing the association to stand out from the background rate. Also, 32 reports of lovastatin-associated blindness are included in the database. The report says that concerns have been raised about the possibility of cataracts with 3 other statins, following the development of lens opacities with high-doses of these drugs in animal studies. Also, optic nerve vacuolisation has been reported in a dog that was administered high-dose atorvastatin.

Singapore⁽²⁾. The Health Sciences Authority in Singapore has suspended the marketing and sale of cerivastatin (Lipobay) following Bayer Corporation's voluntary withdrawal of the agent in Aug 2001 due to concerns of an associated increased risk of rhabdomyolysis. The Pharmacovigilance Unit in Singapore received 4 reports of cerivastatin-induced rhabdomyolysis between December 2000 and June 2001. One of the patients had received cerivastatin and gemfibrozil concomitantly. In all of the cases, the patients had received the recommended daily dose of the agent and rhabdomyolysis had developed within 1 month of starting treatment. In Singapore, the concomitant use of

cerivastatin and gemfibrozil has been listed as a contraindication in the product insert since February 2000, and the maximum approved daily dosage of cerivastatin has been 0.4mg since the launch of the agent in 1998. The Pharmacovigilance unit has also received 2 reports of rhabdomyolysis associated with simvastatin (Zocor), 1 report with atorvastatin (Lipitor) and 1 report with lovastatin.

Reference:

1. *Newsletter of the Indian National Pharmacovigilance Centre* 3(1): 3, Nov 2001
2. *Adverse Drug Reaction News* 3: 2-3, Dec 2001.

STAVUDINE

Safety information updated

Canada, USA. A 'Dear Healthcare Professional' letter has been issued by Bristol-Myers Squibb (BMS), Canada, advising of new safety information to be incorporated into the product monograph for stavudine (Zerit). The information to be added states that reports have been received of rare occurrences of rapidly ascending neuromuscular weakness, mimicking the clinical presentation of Guillain-Barré syndrome (including respiratory failure), in patients with HIV infection receiving stavudine in combination with other antiretrovirals. It says that there have been 22 such reports worldwide since 1994, 7 of which were fatal. Patient exposure to stavudine during this time is estimated at 832 383 patient-years. Most of these cases are said to have been reported in the setting of lactic acidosis or symptomatic hyperlactacidaemia and, in the majority, antiretroviral therapy had been continued in the presence of nonspecific early symptoms of hyperlactacidaemia that preceded the development of neuromuscular signs and symptoms. The company advises that stavudine should be discontinued in patients who

develop motor weakness. The company reminds healthcare providers to be vigilant in identifying early signs of hyperlactacidaemia due to the life-threatening potential of its most extreme manifestation, lactic acidosis syndrome. Early symptoms associated with elevated serum lactate may include generalised fatigue and/or various gastrointestinal, respiratory or neuromuscular symptoms. Patients presenting with such symptoms should have their antiretroviral therapy interrupted and a full medical investigation performed. The company also points out that patients with hyperlactacidaemia may experience persistence or worsening of symptoms despite discontinuation of antiretroviral therapy. The above information from BMS has also been posted on the US FDA's website, on Medwatch.

Reference:

1. 'Dear Healthcare Professional' letter from Bristol-Myers Squibb Company, 6 Mar 2002. Available from URL: <http://www.hc-sc.gc.ca>
2. 'Dear Healthcare Professional' letter from Bristol-Myers Squibb Company, 6 Mar 2002. Available from URL: <http://www.fda.gov>.

ZOLPIDEM

Neurological and psychiatric reactions reported

Australia. During 2001, the Australian Adverse Reactions Advisory Committee (ADRAC) received 72 reports describing 170 adverse reactions associated with the use of zolpidem. Fifty-six of these reports described one or more neurological or psychiatric events, including visual hallucinations, confusion and depression. The committee states that prescribers should be aware that zolpidem may be associated with these events.

Reference:

- Australian Adverse Drug Reactions Bulletin* 21(1): 3, Feb 2002.

Risk/benefit assessment for using praziquantel for the treatment of schistosomiasis in pregnant and lactating women

Schistosomiasis is a parasitic disease caused by five species of the flatworm or blood flukes known as schistosomes. The disease affects over 200 million people and results in excess morbidity and mortality. Animal studies as well as human examples with pregnant women show that schistosomiasis can have dramatic negative effects on both mother and foetus.

Praziquantel is the drug of choice in treating schistosomiasis. However, current drug policies discriminate against the use of praziquantel for the treatment of schistosomiasis in women of child-bearing age. At the beginning of April 2002, an informal consultation took place in WHO, Geneva on the use of praziquantel in lactating and pregnant women.

A thorough review of the non-clinical toxicity and pharmacokinetics of praziquantel was presented, which concluded that the drug lacks significant toxic potential. Furthermore, although no systematic monitoring had been carried out, there was no indication of reproductive toxicity with inadvertent use in clinical practice. The WHO database held in the WHO Collaborating Centre for International Drug Monitoring contains only 208 adverse drug reaction reports for praziquantel none of which are related to reproductive toxicity.

Praziquantel in breast milk was also discussed. It was demonstrated that a suckling infant would ingest a maximum of 0.1% of the weight-adjusted maternal dose; this was regarded as safe.

Conclusions of the consultation may be summarised as follows:

- 1) Given the special schistosome related morbidity of women world wide, and the clear beneficial effect of praziquantel treatment,
 - a) women of child-bearing age should not be excluded from population based chemotherapy programmes for schistosomiasis
 - b) pre and post pubescent females should be included in all schistosomiasis control strategies and specific steps taken to guarantee their coverage.
- 2) All pregnant and lactating women infected with schistosomiasis should be offered immediate treatment.
- 3) All pregnant and lactating women living in areas highly endemic for schistosomiasis, where universal population chemotherapy is employed, should be included and offered treatment.
- 4) In schistosomiasis endemic areas where universal chemotherapy is not implemented, women of child-bearing age (including those pregnant and lactating) should be considered as a high-risk group for morbidity and targeted treatment should be offered to them.
- 5) WHO should encourage control programmes using praziquantel in pregnant women to collect data on the outcome of pregnancy for mother and infant in sufficiently large numbers. This data should be compared with the expected incidence of foetal abnormalities and other negative birth outcomes in the populations concerned.

Last year, the Uppsala Monitoring Centre analyzed the adverse drug reaction (ADR) case reports for some of the drugs in their database. While a definite signal review is not possible at this stage, the analysis definitely highlights some interesting associations. The following section summarizes these associations for proton pump inhibitors and loratadine with male reproductive disorders based on the reports as of 2001.

PROTON PUMP INHIBITORS

- **Testicular pain**

There were 12 reports of testicular pain associated with omeprazole in the database. There were single reports from the UK and New Zealand and the rest were from the USA. The patients were in the age group of 33 to 75 years. The duration of omeprazole use prior to onset of pain was indicated for five patients and varied from 3 days to 7 months. Associated disorders were listed for 5 patients and included breast pain and gynaecomastia (2), scrotal irritation (1), hepatitis (1) and abdominal pain and arthralgia (1). Five patients were taking other medicines and in one patient these included paroxetine and lansoprazole. Three patients improved when omeprazole was withdrawn but three did not and withdrawal information was not provided for the rest.

The Physicians' Desk Reference lists testicular pain as an adverse effect associated with omeprazole use but the relationship to omeprazole has not been determined. These reports with a variable response to withdrawal lend some support to the association. Further evidence that this may be an adverse effect of proton pump inhibitors comes from a well-

documented report for lansoprazole describing a 41 year old male patient who experienced testicular pain, gynaecomastia, peripheral oedema and weight gain with improvement on withdrawal.

- **Gynaecomastia and impotence**

As stated above two patients with testicular pain also had gynaecomastia. In 1992 Lindquist and Edwards⁽¹⁾ described well-documented reports of gynaecomastia and impotence. There are now 200 reports of gynaecomastia with omeprazole i.e. 0.5% of total reports for omeprazole. For lansoprazole the proportion is 0.3% and for pantoprazole 0.3%. For impotence the proportions are omeprazole 0.4%, lansoprazole 0.3% and pantoprazole 0.5%. There are 50 reports of breast pain with omeprazole and 21 reports with lansoprazole.

The database supports a causal association between proton pump inhibitors and gynaecomastia, breast pain and impotence. Testicular pain is also a likely but rare adverse effect.

Reference:

1. Lindquist M, Edwards IR. Endocrine adverse effects of omeprazole. *British Medical Journal* 305: 451-452, 1992.

LORATADINE

Loratadine is a tricyclic antihistamine with selective peripheral H1 receptor antagonist activity. It is indicated for the treatment of allergic rhinitis and other hay fever symptoms. The total number of reports for loratadine is 7937.

- **Prostatic disorder**

There were 5 reports of prostatic disorder and one of aggravated prostatism. All the reports were from the USA. Age was stated for 3 patients, two were aged 80 years and one 75 years. Three improved on withdrawal of loratadine and in one there was no recurrence on rechallenge.

Dechallenge data was not recorded for the other patient. The only associated symptom was insomnia occurring in one patient. All were taking loratadine combined with pseudo-ephedrine.

Recently there were 12 reports of glaucoma with loratadine. These reports as well as the reports of prostatism suggest that loratadine has anti-cholinergic effects. There are also some reports of prostatic disorder for other non-sedating anti-histamines and for dexchlorpheniramine but not for promethazine and diphenhydramine. The Physicians' Desk Reference lists the occurrence of urinary retention in at least one patient taking loratadine. Urinary retention is a good marker of anti-cholinergic activity. The occurrence of urinary retention appears to vary between 0.1% to 0.4% for sedating antihistamines and between 0.2 to 0.3% for 'non-sedating' anti-histamines, suggesting that there may be no difference in the cholinergic activity between preparations. For the long acting form of loratadine however the proportion of urinary retention reports was 1.1%.

International Conference on Harmonization (ICH): Activities in Pharmacovigilance

The International Conference on Harmonization (ICH) of Technical Requirements for the Registration of Pharmaceuticals for Human Use was established in 1990 as a joint regulatory/industry project to improve, through harmonization, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States, in order to make these products available to patients with a minimum of delay. ICH is a joint initiative involving both regulators and industry as equal partners in the scientific and technical discussions of the testing procedures which are required to ensure and assess the safety, quality and efficacy of medicines.

The focus of ICH has been on the technical requirements for medicinal products containing new drugs. The vast majority of those new drugs and medicines are developed in Western Europe, Japan and the United States of America and therefore, when ICH was established, it was agreed that its scope would be confined to registration in those three regions. WHO has the status of observer at the ICH meetings representing the interests of non-ICH countries.

To date, ICH has produced more than 45 guidelines; most of them focus on detailed technical requirements to evaluate the quality, safety and efficacy of products before they are authorized for the market in the three regions.

New objectives

In addition to the initial objectives, the fifth ICH meeting held in Tokyo in May 2001 identified post-marketing surveillance as one of the future objectives for the forum.

Three topics were identified as being possible for harmonization in ICH guidelines: Periodic Safety Update Report (PSUR), Case Management Practices, and Roll out of New Drug Products

These and problems related to these issues were discussed in depth during an informal meeting of the ICH in Brussels, on 4-5 February 2002.

1) Periodic Safety Update Report (PSUR)

The ICH guideline, 'Periodic Safety Update Reports for Marketed Drugs' (Topic E2C) was developed based on the final report of CIOMS (Council for International Organizations of Medical Sciences) Working Group and finalized in the year 1996 to harmonize the frequency of submission and content of safety updates, to avoid duplication of effort and to ensure that important safety data are submitted with consistency to regulatory authorities. Although this guideline describes the format and content of PSUR, there are regional differences in the implementation and utilization of PSUR which poses regulatory difficulties. It is important to harmonize the understanding and development of the PSUR guidance so that, as far as possible, all regions adopt similar reporting procedures, in terms of frequency of reporting, quality of contents etc. This in turn would allow more harmonized regulatory control of drug products.

2) Case Reporting

The Extension of ICH guideline on 'Clinical Safety Data Management: Definitions and Standards for Expedited Reporting' (Topic E2A) to post-marketing should include the proposals contained in the CIOMS V report that addresses the current challenges in pharmacovigilance with some pragmatic solutions. Emphasis should be laid on quality and not the quantity of reports generated and a harmonized core data

sheet should be employed to distinguish between the expected and the unexpected adverse reactions with a product.

3) Safe Rollout of New Drug Products

Safety concerns during the early phase of global marketing of new drug products should be addressed to improve product and public safety. Guidance on study design (criteria for post-marketing commitments) including post-marketing studies, based on pre-marketing data, should be explored. Safety studies on the suspected safety issues at the time of authorization (for example, drug interaction information, pediatric information) should be dealt with in a careful rollout phase that would include risk communications/interactions with health professionals.

A report of this discussion was received by the Steering Committee of the ICH. It agreed to launch two new topics: the development of a further guidance on Periodic Safety Update Reports (PSURs), which will be an addendum to the existing E2C guideline, and a guidance on Good Case Management Practices which will be a follow-up of the E2A guideline. Both are expected to be reviewed in draft form at the next meeting in Washington DC in September 2002. Further discussions are also planned on a third item: Early Phase Post-Marketing Vigilance.

Partnership with WHO

The WHO with its collaborating centre, the Uppsala Monitoring Centre, is the only official body with a truly independent and global perspective on drug safety. ICH's continuing collaboration with WHO, in a complementary fashion, is essential particularly as ICH moves into the area of pharmacovigilance. WHO will continue as an observer at the ICH meetings on any issue related to pharmacovigilance and all ICH countries should be

encouraged to participate more actively in the WHO Programme for International Drug Monitoring. A briefing paper on the activities of the WHO Programme for International Drug Monitoring and a discussion paper on WHO's activities in the area of pharmacovigilance are available from QSM/EDM, WHO.

EVENTS & ANNOUNCEMENTS

- **The 25th Annual Meeting of Representatives of the National Centre participating in the WHO International Drug Monitoring Programme will be held in Amsterdam, Netherlands, from 13-16 October 2002. The local organizer is Dr Kees van Grootheest from Lareb, the Netherlands Pharmacovigilance Foundation.**
- **The WHO-UMC regional training course on 'Pharmacovigilance – the study of adverse drug reactions' will be held in Canberra, Australia, in conjunction with the Australian National Centre from 4-15 November 2002.**