WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

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

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This Newsletter is also available on our Internet website: http://www.who.int/medicines

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In this issue as usual we report regulatory actions taken around the world on grounds of safety issues, among them new restrictions in the use of rosiglitazone, and the market withdrawal of sibutramine. We also give you updates on the safety of several medicines.

The feature article in this issue gives you conclusions from working groups at the thirty-third meeting of representatives of national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring.

We wish all our readers a very good year in 2011, and thank you for your interest in the newsletter.

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Bisphosphonates

Label update for atypical fractures

USA. The United States Food and Drug Administration (US FDA) notified the public that the drug labels of all bisphosphonate products approved for the prevention or treatment of osteoporosis will be revised to include updated information on the risk of atypical fractures of the thigh, known as subtrochanteric and diaphyseal femur fractures. The labels will also include a new Limitations of Use statement that will describe the uncertainty of the optimal duration of use of bisphosphonates for the treatment and/or prevention of osteoporosis. The Agency states that although the optimal duration of bisphosphonate use for osteoporosis is unknown, these atypical fractures may be related to long-term term bisphosphonate use. In addition, a Medication Guide will be required to be given to patients. This Medication Guide will describe the symptoms of atypical femur fracture and recommend that patients notify their health-care professional if they develop symptoms.

The US FDA explains that atypical femur fractures appear to account for less than one percent of all hip and femur fractures overall, and that although it is not clear if bisphosphonates are the cause, atypical femur fractures have been predominantly reported in patients taking bisphosphonates.

Health-care professionals are advised to discontinue potent antiresorptive medicines (including bisphosphonates) in patients who have evidence of a femoral shaft fracture, and to consider periodic re-evaluation of the need for continued bisphosphonate therapy, particularly in patients who have been treated for over five years.

Reference:
FDA Drug Safety Communication, US FDA, 13 October 2010 (www.fda.gov)

Codeine-containing liquid over-the-counter medicines

Advice against use for cough in children under 18 years

UK. Medicines and Healthcare products Regulatory Agency (MHRA) has announced that a UK review on the benefits and risks of over-the-counter (OTC) oral liquid cough medicines containing codeine has concluded that the risks outweigh the benefits in children and young people under 18 years. Therefore, it has been advised that codeine-containing OTC liquid medicines should not be used for cough suppression in children and people younger than age 18 years. In February 2009, the MHRA announced new measures for safer use of OTC cough and cold medicines for children younger than age 12 years.

(See WHO Pharmaceuticals Newsletter No.2, 2009).

***Reference**:*
Drug Safety Update, MHRA, Volume 4, Issue 3, H3 October 2010 (www.mhra.gov.uk).

Gonadotropin-releasing hormone agonists

Label change due to increased risk of diabetes and cardiovascular disease

USA. The US FDA has announced that new safety information on increased risk of diabetes and certain cardiovascular diseases (heart attack, sudden cardiac death, stroke) will be added to the *Warnings and Precautions* section of the drug labels for Gonadotropin-Releasing Hormone (GnRH) agonists. The decision is based on the Agency's review of several published studies. The US FDA states that most of the studies reviewed by the Agency reported small, but statistically significant increased risks of diabetes and/or cardiovascular events in patients receiving GnRH agonists. GnRH agonists are approved to treat the symptoms (palliative treatment) of advanced prostate cancer.

The US FDA advises that although the risk for diabetes and cardiovascular diseases appears to be low in men receiving GnRH agonists for prostate cancer, it is important for health-care professionals to evaluate patients for risk factors for these diseases. Health-care professionals are also advised to monitor blood glucose and/or glycosylated haemoglobin periodically in patients receiving GnRH agonists; to monitor patients for signs and symptoms suggestive of development of cardiovascular disease; to ensure that cardiovascular risk factors such as cigarette smoking, high blood pressure, high cholesterol, high blood sugar, and being overweight

are managed according to current clinical practice.

Reference:
FDA Drug Safety Communication, US FDA, 20 October 2010 (www.fda.gov).

Propoxyphene

Withdrawal due to risk of cardiac toxicity

USA. The US FDA has recommended against continued use of propoxyphene after receiving new data that indicate the risk of cardiac toxicity. Propoxyphene is an opioid pain reliever used to treat mild to moderate pain. The US FDA has announced that the manufacturer Xanodyne Pharmaceuticals Inc. has agreed to withdraw propoxyphene from the United States market at the Agency's request. The Agency also requested that the generic manufacturers of propoxyphene-containing products remove their products. The Agency's recommendation was made based on all available data including new clinical data showing that when propoxyphene was taken at therapeutic doses, there were significant changes to the electrical activity of the heart: prolonged PR interval, widened QRS complex and prolonged QT interval. These changes can increase the risk for serious abnormal heart rhythms. The US FDA concluded that the safety risks of propoxyphene outweigh its benefits for pain relief at recommended doses. Health-care professionals are advised to stop prescribing and dispensing propoxyphene-containing products to patients, to ask patients to discontinue the medicine, and to discuss alternative pain management strategies with their patients.

(Propoxyphene is USAN, dextropropoxyphene is the equivalent INN).

Reports in WHO Global ICSR database, Vigibase:

Dextropropoxyphene

Number of reports (SOC Cardiovascular disorders, general and SOC heart rate and rhythm disorders): 278

Most reported reactions (number of events):

Cardiomegaly:	*26*
Hypertension:	*22*
Hypotension:	*39*
Bradycardia:	*14*
Cardiac arrest:	*146*
Palpitation:	*18*
Tachycardia:	*27*

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for recommendation to withdraw the marketing authorizations for dextropropoxyphene-containing medicines in Europe).

***Reference**:*
MedWatch, Safety Information, US FDA, 19 November 2010 (www.fda.gov).

Rosiglitazone

New restrictions due to risk of cardiovascular events

Canada. GlaxoSmithKline Inc. and Health Canada have informed the public that the Canadian Product Monographs for rosiglitazone-containing products (Avandia® (rosiglitazone), Avandamet® (rosiglitazone and metformin) and Avandaryl® (rosiglitazone and glimepiride)) have been updated to include new restrictions on the use of these medicines, informed consent process and a new boxed warning because of cardiovascular risks.
The rosiglitazone-containing products are now indicated only in patients with type 2 diabetes mellitus for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycaemic control or are inappropriate due to contraindications or intolerance.
The new boxed warning includes the following information.

- Rosiglitazone-containing products, like other thiazolidinediones, can cause fluid retention and congestive heart failure.
- Rosiglitazone-containing products may be associated with an increased risk of cardiac ischemia. These medicines are not recommended in patients with a history of ischaemic heart disease, particularly those with myocardial ischaemic symptoms.

Health-care professionals are advised to counsel new and currently treated patients about the risks of initiating and/or continuing rosiglitazone therapy and obtain their written informed consent.

(See WHO Pharmaceuticals Newsletter No.5, 2010 for information on suspension of marketing authorizations in Europe, new restrictions in the USA and reports in WHO global ICSR database).

***Reference**:*
Advisories, Warnings and Recalls, Health Canada, 18 November 2010 (www.hc-sc.gc.ca).

Saquinavir

Change to prescribing information regarding QT/PR interval prolongation

Europe (1). European Medicines Agency (EMA) has announced that it has completed a review of saquinavir (Invirase®) and its cardiovascular safety. The Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on saquinavir and the potential risk of arrhythmia, and concluded that the benefit of the medicine continues to outweigh its risks. However, the CHMP has recommended that treatment-naïve patients should take a reduced dose of saquinavir during the first week of treatment, as a precautionary measure. Ritonavir-boosted saquinavir in combination with other antiretroviral medicines is indicated for the treatment of HIV-infected adult patients.

EMA explains that the CHMP started the review following the results of a study conducted by the marketing authorisation holder, showing that saquinavir prolonged the QT and PR intervals in healthy volunteers. In June 2010, the Committee recommended restrictions on the use of saquinavir, including a contra-indication in patients at high risk of arrhythmia and in patients using other medicines that may cause QT or PR prolongation, warnings for patients at moderate risk of arrhythmia, and recommendations to perform electrocardiogram monitoring.

In October 2010, the CHMP conducted a full review of the benefit-risk balance of saquinavir. It was noted that the effectiveness of saquinavir has been demonstrated in several clinical studies. Although the dedicated study in healthy volunteers did show QT and PR interval prolongation, this signal has not been confirmed in post-marketing safety reports on the medicine since the medicine was first authorised in 1996. The risk of QT and PR prolongation has been shown to be dose dependent, and is expected to be higher in patients who have not been treated with any anti-HIV medicines before. Therefore, to minimise the potential cardiovascular risk, the CHMP recommended a reduced dose for these patients in the first week of treatment.

Canada (2). Hoffmann-La Roche Limited and Health Canada notified health-care professionals that the warnings regarding QT/PR interval prolongation have been strengthened in the Canadian Product Monograph for saquinavir mesilate (Invirase®). The main updates include the following:

- An electrocardiogram should be completed prior to initiation of ritonavir-boosted saquinavir;
- Patients with a QT interval greater than 450 msec should not use ritonavir-boosted saquinavir;
- An on-treatment electrocardiogram is recommended after three to four days of treatment. If a patient's QT interval is greater than 20 msec above pre-treatment values, or greater than 480 msec, then ritonavir-boosted saquinavir should be discontinued;
- Caution is advised when co-administering ritonavir-boosted saquinavir and other therapies that may increase the QT interval. Electrocardiogram monitoring should be performed in this patient population.

USA (3). The US FDA has notified the public that new safety information has been added to the label of saquinavir (Invirase®), describing the risk of prolongation of the PR or QT intervals when saquinavir is used with ritonavir (Norvir®). Saquinavir and ritonavir are given together to treat HIV infection. In addition, the US FDA will require that a Medication Guide, which will include information on the risk of abnormal heart rhythms, be given to patients.

The US FDA explains that this new information was derived from a clinical study designed to study a drug's impact on the electrical activity of the heart. A prolonged QT interval can lead to torsades de pointes. A prolonged PR interval can lead to complete heart block. Torsades de pointes and complete heart block have been reported in patients taking saquinavir with ritonavir.

The Agency advises that patients at particular risk are those with underlying heart conditions or those who have existing heart rate or rhythm problems. Health-care professionals are advised to perform an electrocardiogram prior to initiation of treatment, and to consider whether ongoing electrocardiogram monitoring is appropriate for your patient and when it should be done.

Reports in WHO Global ICSR database, Vigibase:

Saquinavir

Number of reports (SOC heart rate and rhythm disorders): 71

Most reported reactions (number of events):

Bradycardia:	*10*
Cardiac arrest:	*12*
Arrhythmia ventricular:	*9*
Extrasystoles:	*12*
QT prolonged:	*7*
Palpitation:	*12*
Tachycardia:	*10*
Torsade de pointes:	*12*

(See WHO Pharmaceuticals Newsletters No.5, 3 and 2, 2010 for warnings about risk of QT and PR interval prolongation in Canada, the UK and the USA).

References:

(1) Press release, Questions and answers, EMA, 21 October 2010 (www.ema.europa.eu).
(2)Advisories, Warnings and Recalls, Health Canada, 2 November 2010 (www.hc-sc.gc.ca).
(3) FDA Drug Safety Communication, US FDA, 21 October 2010 (www.fda.gov).

Sibutramine

Market withdrawal due to risk of serious cardiovascular events

Australia (1). Therapeutic Goods Administration (TGA) has announced that Abbott Australasia will cease supply of sibutramine (Reductil®) in Australia from 9 October 2010. Sibutramine is indicated for weight loss. This follows an analysis of the results of the Sibutramine Cardiovascular OUTcomes (SCOUT) study, which showed a higher rate of cardiovascular events in obese and overweight patients using sibutramine than in patients managing their weight through exercise and diet alone.

SCOUT was conducted as a post-market requirement to evaluate the cardiovascular safety of long-term sibutramine use, after the European approval of the medicine. The TGA also states that the increased risk of the cardiac events is not significantly different across various patient subgroups in the study, including the subgroup that most closely approximates the approved use of sibutramine in Australia.

Canada (2). Health Canada has informed the public of voluntary withdrawal of sibutramine (Meridia® and Apo-sibutramine®) by Abbott Laboratories and Apotex Inc. The decision was made based on data from the SCOUT trial. Health Canada states that despite risk mitigation measures, there continues to be concern of an increased risk of heart-related adverse events, particularly as people at risk of cardiovascular disease may not have symptoms. In light of this concern and the accumulating scientific evidence on the safety and efficacy of sibutramine, it has been concluded that the benefits no longer outweigh the risks for sibutramine.

Prescribers are advised not to issue any further prescriptions for sibutramine. Patients currently taking sibutramine are advised to contact their healthcare practitioner regarding potential alternatives.

USA (3). The US FDA and Abbott Laboratories notified health-care professionals and patients about the voluntary withdrawal of sibutramine (Meridia®) from the United States market because of clinical trial data indicating an increased risk of heart attack and stroke. The Agency states that its recommendation for market withdrawal is based on new data from the SCOUT trial. SCOUT demonstrated a 16% increase in risk of major adverse cardiovascular events (a composite of non-fatal heart attack, non-fatal stroke, resuscitation after cardiac arrest and cardiovascular death) in patients treated with sibutramine compared to patients taking a placebo. At the end of the trial (60 months), patients in the sibutramine group lost a small amount of body weight compared to patients in the placebo group. The US FDA has concluded that the risk for an adverse cardiovascular event from sibutramine in the population studied outweighed any benefit from the modest weight loss observed with the medicine.

Physicians are advised to stop prescribing and dispensing sibutramine to their patients. Patients are advised to stop taking sibutramine and to talk to their health care provider about alternative weight loss and weight loss maintenance programmes.

(See WHO Pharmaceuticals Newsletter No.1, 2010 for suspension of marketing authorizations in the European Union and reports in WHO Global ICSR database.)

References:
(1) Safety information, Alerts/advisories, TGA, 8 October 2010 (www.tga.gov.au).
(2) Advisories, Warnings and Recalls, Health Canada, 18 October, 13 October and 8 October 2010 (www.hc-sc.gc.ca).
(3) FDA Drug Safety Communication, US FDA, 8 October 2010 (www.fda.gov).

Tinzaparin sodium

Use in elderly patients with renal impairment is not recommended

Canada. Health-care professionals have been advised that tinzaparin sodium (Innohep®) is not recommended in elderly patients over 70 years of age with renal impairment. In addition, tinzaparin sodium should be used with caution in patients with moderate to severe renal impairment, and in all cases of impaired renal function, patients should be closely monitored. Tinzaparin sodium is authorized for the prevention of post-operative venous thromboembolism (VTE) in patients undergoing orthopaedic surgery and in patients undergoing general surgery who are at high risk of developing post-operative VTE, the treatment of deep vein thrombosis and/or pulmonary embolism, and the prevention of clotting in indwelling intravenous lines for haemodialysis and extracorporeal circulation in patients without high bleeding risk. The company explains in the Dear Health Care Professional letter that a clinical study (Innohep in Renal Insufficiency Study (IRIS)) was stopped prematurely due to an interim finding of an increase in all-cause mortality in patients who received tinzaparin sodium compared to unfractionated heparin. The study involved the use of therapeutic doses of tinzaparin sodium for the treatment of acute VTE in elderly patients with renal impairment. The Canadian Product Monograph has been revised accordingly.

(See WHO Pharmaceuticals Newsletter No.1, 2009 for ongoing safety review on an increased risk of mortality in elderly patients in the USA.)

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 October 2010 (www.hc-sc.gc.ca).

Zoledronic acid

Risk of renal dysfunction

Canada. Health-care professionals have been warned that zoledronic acid (Aclasta®) for intravenous infusion has been associated with renal dysfunction manifested as deterioration in renal function and in rare cases, acute renal failure. In a Dear Health Care Professional letter, Novartis Pharmaceuticals Canada Inc. says that as of 30 April 2010, the company has received 265 spontaneous reports of renal impairment following administration of zoledronic acid, corresponding to a reporting rate of approximately 20 cases per 100 000 patient-years of exposure. The letter states that renal failure requiring dialysis or with a fatal outcome has occurred, especially in patients with history of renal impairment or other risk factors. Risk factors include advanced age, concomitant nephrotoxic medicinal products, concomitant diuretic therapy or dehydration occurring after administration of zoledronic acid. The Canadian Product Monograph has been revised to include measures to minimize the risk of renal adverse reactions. As a precaution, health-care professionals are advised that zoledronic acid should not be used in patients with severe renal impairment.

(See WHO Pharmaceuticals Newsletters No.4 and No.3, 2010 for warnings about adverse effects on renal function in New Zealand, the UK and reports in WHO Global ICSR database)

Reference:
Advisories, Warnings and Recalls, Health Canada, 14 October 2010 (www.hc-sc.gc.ca).

Fibrates

Recommendation for use as second-line treatment

Europe. EMA has announced that a review of the safety and effectiveness of fibrates has been completed. The CHMP has concluded that the benefits of the four fibrates bezafibrate, ciprofibrate, fenofibrate and gemfibrozil continue to outweigh their risks in the treatment of patients with blood lipid disorders. However, the CHMP recommended that fibrate-containing medicines should not be used as first-line treatment, except in patients with severe hypertriglyceridaemia and in patients for whom statins are contra-indicated or who cannot tolerate them. This confirmed the conclusions of the review by the CHMP's Pharmacovigilance Working Party (PhVWP) in 2005.

Fibrates are used to lower level of lipids such as triglycerides and cholesterol in the blood, for patients in whom dietary restrictions and exercise have not been enough. The CHMP also noted that there were new data for fenofibrate that supported a change to the PhVWP recommendations, and recommended that fenofibrate can also be used together with a statin in some circumstances when a statin on its own has not been enough to completely control blood lipid levels.

Prescribers are advised to review the treatment of patients who are receiving fibrates to help control their lipid levels to ensure that patients are receiving the most appropriate treatment.

Reference:
Press release, Questions and answers, EMA, 22 October 2010 (www.ema.europa.eu).

Influenza vaccine

Reports of suspected adverse reactions

Australia. Therapeutic Goods Adminstration (TGA) informed the public of suspected adverse reactions to Pandemic (H1N1) 2009 influenza vaccine, Panvax®. From 30 September 2009 to 17 September 2010, a total of 1960 suspected side effects had been reported to the TGA following vaccination with Panvax® in Australia. The Agency states that the great majority of reported side effects have been mild and common problems such as headache, gastrointestinal upset, and soreness, swelling, or redness at the injection site.

As a result of analysis of the rate of febrile convulsions associated with Panvax, the TGA says that the estimated rate of febrile convulsions with Panvax lies between 0.08/1000 and 0.18/1000, which equates approximately to a rate of between one in 5000 and one in 12,000 doses administered, and that this estimate is within the predicted rate for influenza vaccines.

With regard to a possible association with the development of Guillain-Barré syndrome (GBS), the TGA has concluded that there is no evidence of an increased rate of GBS in people receiving Panvax®. Regarding reports of possible anaphylaxis following vaccination with Panvax®, the TGA has concluded that, based on distribution figures for Panvax®, the current observed rate of anaphylaxis is within the range expected for post-immunisation.

The TGA states that the Agency's assessment remains that Panvax® is a safe, effective vaccine for prevention of the H1N1 influenza.

Reference:
Safety information, Alerts/advisories, TGA, 6 October 2010 (www.tga.gov.au)

Statins

Risk of interstitial lung disease

Canada. Health Canada alerted health-care professionals to the risk of interstitial lung disease (ILD) associated with statins (cholesterol-lowering medicines). In the *Canadian Adverse Reaction Newsletter,* Health Canada states that during the last 15 years, 29 cases of interstitial lung disease suspected of being associated with statins have been published. Of these cases, 16 described a positive dechallenge with or without immunosuppressive treatment, and 3 cases described a positive rechallenge. As of 31 March 2010, Health Canada received 8 adverse reaction reports of ILD, or pathologies associated with ILD, suspected of being associated with the following statins: atorvastatin (3), pravastatin (2), rosuvastatin (2) and simvastatin (1). Pulmonary fibrosis (3), ILD or interstitial pneumonia (2), sarcoidosis (1), Churg–Strauss syndrome (1) and polyarteritis nodosa with severe coughing (1) were described in the reports. Out of the eight cases, six were reported as serious. In two cases, the pulmonary condition improved after the statin was stopped and the ILD treated. Health Canada advises that drug-induced ILD is a rare but serious adverse reaction and may be life- threatening, and that it can mimic other ILDs and is considered a condition of

exclusion rather than a specific entity.

(See WHO Pharmaceuticals Newsletter No.1, 2010 for updates to product safety information of statins in the UK.)

***Reference**:*
Canadian Adverse Reaction Newsletter, Health Canada, Volume 20, Issue 4, October 2010 (www.hc-sc.gc.ca).

Tamoxifen

Drug interactions with CYP2D6 inhibitors

UK. MHRA has advised that CYP2D6 genetic polymorphisms and concomitant use of potent CYP2D6 inhibitors may be associated with variability in clinical response in patients treated with tamoxifen for breast cancer. Therefore, the Agency has recommended that concomitant use of medicines that inhibit the CYP2D6 enzyme, such as paroxetine, fluoxetine, bupropion, quinidine and cinacalcet, should be avoided whenever possible in patients treated with tamoxifen.

Tamoxifen is a selective oestrogen-receptor modulator indicated for palliative and adjuvant treatment of oestrogen-receptor-positive breast cancer in premenopausal and postmenopausal women. Tamoxifen is metabolized to endoxifen, which is the active agent, and this metabolic process is mediated by the CYP2D6 enzyme. The MHRA explains that in patients with inherited non-functional alleles of the CYP2D6 gene (poor metabolisers) or in patients concomitantly treated with CYP2D6 enzyme inhibitors, concentrations of the tamoxifen metabolites that most strongly bind to the oestrogen receptor may be reduced. With regard to the effect of genetic polymorphisms, the Agency says that the evidence linking various poor metaboliser genotypes and tamoxifen treatment outcomes is mixed and inconclusive. Therefore, there is no current recommendation for genetic testing before treatment with tamoxifen.

Reference:
Drug Safety Update November 2010, Volume 4, Issue 4, A1, MHRA (www.mhra.gov.uk)

Thirty-third annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring

1 - 3 November 2010

The annual meeting was held in Accra, Ghana. Eight working groups were set up to discuss issues related to the development of pharmacovigilance. Several recommendations were made following these discussions.

The role of pharmacovigilance centres in preventing medication errors

The working group discussed the scope and limits of pharmacovigilance (PV) centres in preventing medication errors and how PV centres can have proactive role in preventing medication errors.

The working group recommended the following:

- National PV policies should include medication error issues as part of functions of PV centres.
- Standardized definitions/terminologies for medication errors are needed.
- Existing tools should be modified to capture specific information on medication errors.
- National centres should advocate for reporting of medication errors even when they do not lead to adverse events.
- Medication errors should be incorporated into PV training curricula for students and in-service training modules for health-care professionals.

How to improve the quality of individual case safety reports (ICSRs)

This working group looked at problems of the quality of ICSRs and possible solutions. First a 'good quality' ICSR has to be defined. Many reporters are not very used to reporting ICSRs and may not include relevant information such as laboratory test results in their reports, which would allow better causality assessments.

The working group suggested that possible solutions could be: improved design of reporting forms, and analysis and review of national reporting requirements and practice. The Uppsala Monitoring Centre (UMC) has set up a tool for the analysis of completeness and quality of ICSRs submitted to the international PV database which may be helpful in this respect. It may be possible to identify different quality problems in reports from different groups of reporters (i.e. company reports, direct health-care professionals' reports and consumer reports) and address these separately.

Establishing pharmacovigilance centres: difficulties and solutions

This working group discussed common problems and challenges when setting up or strengthening a PV centre and how to address these. Some of the problems identified were: underreporting, low quality of adverse drug reaction (ADR) reports, shortage of qualified staff at national centres, lack of funding of PV centres, lack of interaction with the regulatory authority, the government and other policy makers, and limitation of the legislation base.

In order to enhance reporting and a 'notification culture', the working group proposed the following actions:

- to include PV training in undergraduate and postgraduate curricula of all health-care professionals, including physicians, pharmacists and nurses;
- to establish active surveillance components, specifically to use public health programmes and the Global Fund PV initiative for the incorporation of PV into the national health-care system;
- to enhance PV promotional activities, especially by engaging professional organizations of health-care providers, internet facilities, mass-media, professional conferences etc.;
- to motivate and stimulate reporting by providing feedback;
- to make reporting mandatory for health-care professionals and the industry.

The working group also considered several funding resources to tackle lack of funding of PV centres; government funding (minimal financing), regulatory resources such as fees, the Global Fund, PEPFAR and similar initiatives, and support by non-profit organizations.

AEFIs: causality assessment and signal detection

It is important to ensure the continued safety of vaccines by monitoring Adverse Events following Immunization (AEFIs). Vaccine-related adverse events that are not rapidly and effectively dealt with can undermine confidence in a vaccination programme and ultimately have dramatic consequences for immunization coverage and disease incidence. It is therefore imperative that methods for reporting ADRs to vaccines, causality assessment and signal detection of AEFIs are in place within PV systems.

Even though most countries have systems in place for AEFI reporting, in many countries there is no proper synergy as regards AEFI reports between the National Regulatory Authorities (NRA), National Immunization Programs (NIP) and PV centres.

The working group recommended:

- Effective communication and collaboration between regulatory authorities, national PV centres and national immunization programs is key to monitoring vaccine safety.
- Standard operating procedures and guidelines need to be developed to make channels of communication clearer.
- The public and the media should be included in any collaborative efforts to monitor AEFIs.

Optimizing pharmacovigilance activities to fight substandard and poor quality medicines

The problem of poor quality, contaminated and substandard medicines is a challenge and systems need to be put in place for the prompt identification and withdrawal of such medicines from the market.

This working group discussed how PV activities can be extended to tackle these issues.

Recommendations:

- PV centres could be the first point of call for reporting sub-standard and poor quality medications.
- Tools need to be redesigned for data collection to make provisions for the reporter to indicate substandard medicines, medication errors (see related working group report), drug abuse etc.
- Advocacy, education and training and timely information dissemination are key in merging efforts to detect ADRs along with fighting poor quality and sub-standard medicines.
- Effective collaborations with various parties will be important in achieving and sustaining these initiatives.

Building human resource capacity for pharmacovigilance

In many national centres PV activities are undertaken by staff that are involved in other areas and therefore cannot focus their efforts on PV and are not adequately trained for this role.

Many PV centres also face the problem of high staff turnover.

The working group discussion centred on who should be trained, competencies needed and who should be responsible for building and financing human resource capacities in PV centres.

Recommendations:

- National centres should have a minimum qualification/skill profile for PV personnel
- PV modules should be included in the training curricula of various health-professionals to give basic awareness of medicine safety issues
- Training packages should be developed for specific and continuous development of staff working in PV. Developing these training curricula will require cooperation with WHO collaborating centres for PV, academia and the use of both internal and external PV consultants
- PV centres should include resources for training within their budgetary requirements for pharmacovigilance.

How to improve awareness of drug safety issues: social marketing of PV

PV in most countries is not well publicized and there is a general lack of understanding of the basics of this concept. Social marketing involves selling "the need for" and "the benefits of" PV to various parties with the aim that they adopt desired behaviours to enhance drug safety.

Recommendations:

- Marketing of PV should be geared towards behavioural changes that will promote ADR reporting. PV marketing should be geared not only to health-professionals but also to the general public.
- Marketing can be done via various means, such as through the media and other public initiatives.
- The impact of any PV marketing efforts should be measured by analyzing prescription data before and after, analyzing media coverage and assessing behavioural changes.

Good practice of pharmacovigilance inspections/assessments.

Conducting PV inspections is key to ensuring best practices in pharmacovigilance.

PV inspections are currently only conducted by a limited number of countries. The power to carry out PV inspections is generally a legal power, so it is enforced by the National Regulatory Authority (NRA), which may be separate from the PV centre. Also, the targets for inspection are therefore those that are regulated by the NRA, generally pharmaceutical companies rather than individual health professionals. It is important however to note that definitions of PV inspections will vary from country to country.

PV inspections can be conducted on a 'routine' (for example, all new companies should be inspected) or when needed (for example, when an anomaly is detected) basis. Based on the experience of countries that have recently commenced PV inspections, it was suggested that a pragmatic approach is that countries start by setting a level of PV inspections which they have the capacity to perform, for example to inspect a certain number of facilities per year.

The working group discussed recommendations for the coordination, conduct and procedures for carrying out PV inspections.

Recommendations:

- National Regulatory authorities (NRA) should take the responsibility of carrying out PV inspections. Collaborations between the NRA and national PV centres will be important in instances where the national PV centre is not part of the regulatory authority.
- Guidelines and procedures need to be developed for carrying out PV inspections and the WHO could take the lead on this together with countries that already have established procedures for PV inspections.