

# WHO PHARMACEUTICALS NEWSLETTER



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

*The aim of this 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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## No. 4, 2007

### News & Issues

In addition to the drug safety and regulatory sections, two feature items may be of special interest to readers in this issue: a brief overview of the ATC/DDD course offered by the WHO Collaborating Centre in Oslo, Norway and a summary of the meeting of the Global Advisory Committee on Vaccine Safety. Including these feature items is in keeping with our promise to bring you more information on vaccine safety and on the work of our Norwegian Collaborating Centre. We look forward to your comments.

Three meetings are due in October in pharmacovigilance: the Annual Meeting of National Centres participating in the WHO Programme for International Drug Monitoring will be held in Buenos Aires, 11-13 October. We hope that the meeting this year will be just as well attended as in the previous years. Working group exercises at the meeting will cover the areas of information access, medicine safety in special populations, and methodologies to complement spontaneous adverse drug reaction reporting.

The 22<sup>nd</sup> Meeting of the WHO International Working Group for Drug Statistics Methodology will be held in Oslo, Norway, 23-25 October, 2007. The meeting will be preceded by the 25<sup>th</sup> anniversary celebration of the Norwegian Centre, the WHO Collaborating Centre for Drug Statistics Methodology. The anniversary celebration will be marked by several presentations including one by Dr Lembit Rago, Coordinator, Quality Assurance and Safety: Medicines, WHO.

The CIOMS/WHO working group for vaccine pharmacovigilance will meet 29-30 October, in Washington, USA. This working group was created in November 2005 to develop general definitions focused on Vaccine Pharmacovigilance. The working group will contribute to the development, review, evaluation and approval of definitions on adverse events following immunization.

We will bring you highlights from these meetings in our later issues of the newsletter.

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## Ceftriaxone

### Some deaths due to calcium-ceftriaxone precipitates

**USA.** Roche USA has issued a 'Dear Health-care Professional' letter to advise that the prescribing information of ceftriaxone sodium (Rocephin) for injection has been updated with information on the potential risks associated with the concomitant use of ceftriaxone with calcium and calcium-containing products. The company says that over the past few years, there have been isolated reports worldwide of neonatal deaths associated with calcium-ceftriaxone precipitates in the lungs and kidneys. In some cases, the ceftriaxone and calcium-containing products were administered at different times and by different routes. Ceftriaxone is a third generation broad spectrum cephalosporin, an antibiotic effective against gram positive and gram negative bacteria. Roche advises that the Contraindications, Warnings, Precautions, Adverse Reactions and Dosage and Administration sections of the ceftriaxone prescribing information have been updated.

According to Roche the revised prescribing information aims to more prominently reinforce that hyperbilirubinaemic neonates, especially those who are premature, should not receive ceftriaxone. The updated labelling advises that ceftriaxone must not be mixed or administered simultaneously with calcium-containing solutions or products, even via separate infusion lines. Furthermore, calcium-containing solutions or products must not be administered within 48 hours of the last ceftriaxone administration.

#### Reference:

'Dear Health-care Professional' letter from Roche Laboratories Inc., June 2007 ([www.fda.gov](http://www.fda.gov)).

## Cinacalcet

### Labelling updated for restrictions in use

Canada. Amgen Canada Inc., in consultation with Health Canada, has issued a 'Dear Health-care Professional' letter and a Public Communication that cinacalcet (Sensipar) is no longer indicated in the treatment of secondary hyperparathyroidism in patients with chronic kidney disease (CKD) who are not receiving dialysis. The use is now restricted for the treatment of secondary hyperparathyroidism in patients with CKD who are receiving dialysis. This restriction follows study results involving cinacalcet recipients with secondary hyperparathyroidism and CKD which showed that patients not receiving dialysis were more likely to develop serum calcium levels below the lower limit of the normal range (8.4 mg/dL) compared with those receiving dialysis. Furthermore, results of a third study initiated by Amgen showed that the incidence of calcium levels below 8.4 mg/dL was consistent with the previous results. Based on these findings, the Product Monograph will be updated. Amgen advises that patients receiving cinacalcet for secondary hyperparathyroidism who are not receiving dialysis should contact their doctor immediately. The company emphasizes that patients should not stop taking cinacalcet without first contacting their doctor.

#### Reference:

'Dear Health-care Professional' letter from Amgen Canada Inc., 19 June 2007 ([www.hc-gc.sc.ca](http://www.hc-gc.sc.ca)).

## Edaravone

### Report of fulminant hepatitis

**Japan.** A new warning about possible fulminant hepatitis has been added to the precautions for edaravone (Radicut) by the Japanese Ministry of Health, Labour and Welfare. Edaravone was approved for use in Japan in 2001 as a product to protect the brain cells of patients who have suffered a stroke, or a restriction of blood to the brain. The possibility of liver disorders, including jaundice and standard hepatitis, is already included in the precautions section of the product label. But the current update was prompted by six case reports of fulminant hepatitis (one fatal) associated with edaravone between April 2003 and February 2007.

#### Reference:

*Reactions Weekly*, 1159:3, 7 July 2007 ([www.adisonline.com](http://www.adisonline.com)).

## Piroxicam

### Restrictions in use

**Europe.** The European Medicines Agency (EMA) has recommended restrictions on the use of piroxicam-containing medicinal products because of the risk of gastrointestinal side effects and serious skin reactions. The Agency's Committee for Medicinal Products for Human Use (CHMP) has determined that piroxicam should no longer be used for short-term painful and inflammatory conditions. Piroxicam can still be prescribed to relieve the symptoms of osteoarthritis, rheumatoid arthritis and ankylosing spondylitis, but should not be used as a first-line treatment for these disorders. Piroxicam should be initiated by a physician with experience in the treatment of such conditions and the drug should be used at the lowest dosage

(no more than 20 mg/day) for as short a time as possible. Treatment should be reviewed after 14 days. Topical medications containing piroxicam are not included in the new restrictions.

*Reports in the WHO database:*

Gastrointestinal system disorders (General) 6692\* (for whole GI system)

gastritis	224
GI haemorrhage	1167
haematemesis	568
melaena	1003
abdominal pain	764
dyspepsia	503
nausea	472
gastric ulcer	522
gastric ulcer haemorrhagic	413
skin disorder	26

**Reference:**

Press Release. EMEA, 25 June 2007 ([www.emea.europa.eu](http://www.emea.europa.eu)).

## Rimonabant Contraindicated in patients with major depression

**Europe.** The European Medicines Agency (EMA) has announced that rimonabant (Acomplia) is contraindicated in patients with ongoing major depression or who are being treated with antidepressants because of the risk of psychiatric adverse effects. Rimonabant is a cannabinoid receptor antagonist and has been authorized as an adjunct to diet and exercise for the treatment of obese or overweight adult patients. The EMA had previously warned doctors in the European Union about the risk of psychiatric adverse effects with rimonabant. The Agency's Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on psychiatric adverse effects with rimonabant that it received from Sanofi-aventis and has concluded that

- the benefits of rimonabant outweigh the risks, except in patients who have ongoing major depression or who are receiving antidepressants. The CHMP recommends adding a warning to the product label that the drug should be discontinued if a patient develops depression;
- the risk of depression is approximately doubled in patients receiving rimonabant compared with obese or overweight patients not receiving the drug, and this could lead to suicidal ideation or even suicide attempts in a small minority of cases.

The CHMP recommends strengthening the product label with information about the psychiatric effects and adding a warning that the drug should be discontinued if a patient develops depression.

**Reference:**

Press Release. EMEA, 18 July 2007 ([www.emea.europa.eu](http://www.emea.europa.eu)).

## Tegaserod Suspended in China; withdrawn in Switzerland; permitted for restricted use in the USA

**China (1).** The production, sale and use of tegaserod (Zelnorm) have been suspended by the Chinese State Food and Drug Administration (SFDA). Tegaserod was originally authorized for the treatment of symptoms associated with irritable bowel syndrome in women. The drug has been associated with an increased risk of strokes and heart attacks, this being the reason for the SFDA decision. According to the SFDA, local and international reports of adverse reactions suggest a negative benefit-risk balance for tegaserod: the risks of treatment with tegaserod

outweigh the possible benefits for some patients. 98 adverse reaction reports involving tegaserod have been received by the National Centre for Adverse Drug Reaction Monitoring since the product was first marketed in China in 2003. Major reactions were reported to be diarrhoea and nausea, but there was one case of tachycardia, two involving heart palpitations and one case of low blood pressure.

**Switzerland (2).** The Swiss Institute of Therapeutic Products, Swissmedic has declined to extend the marketing authorization for tegaserod (Zelmac) in Switzerland after a new analysis of clinical data showed that tegaserod had an increased risk of cardiovascular disorders compared with placebo. Tegaserod was authorized towards the end of October 2001 in Switzerland in the treatment of irritable bowel syndrome in women. Swissmedic advises that tegaserod has an unfavourable risk-benefit ratio. Novartis Pharma Schweiz AG will inform health-care professionals of the withdrawal in Switzerland.

**USA (3).** The United States Food and Drug Administration (US FDA) is permitting the restricted use of tegaserod (Zelnorm) as an investigational new drug for the treatment of irritable bowel syndrome with constipation, and chronic idiopathic constipation. The use of tegaserod (Zelnorm) for such treatment is restricted to women aged < 55 years whose physicians decide that treatment with tegaserod is medically necessary. The FDA previously suspended the sales and marketing of tegaserod following a safety analysis that demonstrated an increased risk of myocardial infarction, stroke and unstable angina associated with tegaserod, compared with placebo (see WHO Pharmaceuticals Newsletter No. 3, 2007).

*Reports in the WHO database:*

Tegaserod (Zelmac): Cardiac failure - 3; myocardial infarction - 3

Tegaserod (Zelnorm):

Hypotension - 27;

diarrhoea - 406; palpitation - 36;

tachycardia - 39

#### **References:**

1. *Reactions Weekly*, 1157:3, 23 June 2007

([www.adisonline.com](http://www.adisonline.com))

2. *Journal Swissmedic*, p342, June 2007

([www.swissmedic.ch](http://www.swissmedic.ch))

3. *FDA News. U.S. Food and Drug Administration*, 27 July 2007

([www.fda.gov](http://www.fda.gov))

## **Thiazolidinedione antidiabetics**

### **Boxed warning on label about heart failure risk**

**USA.** The US FDA, based on a review of post-marketing adverse event reports, has decided that an updated label with a boxed warning on the risks of heart failure is needed for all thiazolidinedione class of antidiabetic drugs. This class includes rosiglitazone (Avandia), pioglitazone (Actos), rosiglitazone and glimepiride (Avandaryl), among others. FDA's review of the post-marketing adverse event reports found cases of significant weight gain, and edema, both of which are warning signs of heart failure; some reports were associated with poor treatment outcomes, including death, when treatment was continued. The strengthened warning advises health-care professionals to observe patients carefully for the signs and symptoms of heart failure, including excessive and rapid weight gain, shortness of breath, and edema after starting drug therapy. Patients with these symptoms who develop heart failure should receive appropriate management of heart failure and, use of the thiazolidinedione antidiabetic drug should be reconsidered. The warning also states that these drugs should not be used by people with serious or severe heart failure.

The issue of whether rosiglitazone increases the risk of heart attacks or not is still unresolved (see WHO Pharmaceuticals Newsletter No. 3, 2007). The FDA's review of this issue is ongoing. In the meantime the Agency advises that rosiglitazone (Avandia) will continue to be marketed with a label that includes information on the risk of heart attacks (ischemia) with the product.

*Reports in the WHO database for rosiglitazone:*

Cardiac Failure	803
Myocardial Infarction	163
Cardiovascular Disorders (as a term)	2

#### **Reference:**

*FDA News. U.S. Food and Drug Administration*, 14 August 2007 ([www.fda.gov](http://www.fda.gov))

## **Warfarin**

### **Label to explain influence of genetic makeup on drug response**

**USA.** The US FDA has approved an updated labelling for warfarin (generic versions and the proprietary brand, Coumadin) to explain that people's genetic makeup may influence how they respond to the drug. The current labelling changes are based on an analysis of recent studies that found people respond to the drug differently based, in part, on whether they have variations of certain genes. Warfarin is a blood thinning drug and is used to prevent blood clots, heart attacks and strokes. It is a difficult drug to use because the optimal dose varies and depends on many risk factors including a patient's diet, age and the use of other medications. Patients who take a dose larger than they can tolerate are at risk of life-threatening bleeding. On the other hand, too low a dose can leave patients at risk of blood clots. Research has shown that some of the unexpected

response to warfarin depends on a patient's variants of the genes CYP2C9 and VKORC1. Genetic testing can identify who has these genetic variants. The new updated label for warfarin will highlight the opportunity for health-care providers to use genetic tests to improve their initial estimate of what is a reasonable warfarin dose for individual patients. According to the US FDA, this update is a step towards personalized medicine, to get the right drug in the right dose for the right patient.

#### **Reference:**

*FDA News. U.S. Food and Drug Administration*, 16 August 2007 ([www.fda.gov](http://www.fda.gov)).

## Colistimethate Premixed formulations must be administered promptly

**USA.** The US FDA is investigating a possible association between the use of a liquid colistimethate sodium solution that had been premixed for nebuliser inhalation, and the death of a patient with cystic fibrosis (CF). Colistimethate is used to treat infections caused by certain types of bacteria, including the bacteria *Pseudomonas aeruginosa* which is known to cause serious lung infections in patients with CF. In the reported death, the pharmacy-prepared colistimethate solution had been dispensed, as prescribed, in premixed vials, ready for use. However, within hours, the patient developed respiratory distress that progressed to acute respiratory failure. The patient had copious thin, pink pulmonary secretions and was admitted to an ICU. A CT scan showed ground glass infiltrates indicative of acute respiratory distress syndrome. Approximately 19 days later, the patient died from multiorgan system failure. Colistimethate is FDA-approved for IM or IV injection but is not approved as a liquid to be inhaled via a nebuliser. In the treatment of CF patients with pseudomonas infections, however, colistimethate is frequently mixed with sterile water to form a solution for nebulisation. The process results in spontaneous hydrolysis of colistimethate to the bioactive form, colistin, a component of which, polymyxin E1, is toxic to lung tissue. Storage of a premixed liquid formulation of colistimethate for longer than 24 hours can result in increased colistin concentrations in the solution and increase the potential for lung toxicity. The FDA recommends that, to avoid this toxicity, the product should be administered

promptly after it has been mixed. Patients are advised to discard any unused vials of ready-to-use, premixed liquid forms of colistimethate.

**Reference:**  
*Public Health Advisory. U.S. Food and Drug Administration, 28 June 2007 ([www.fda.gov](http://www.fda.gov))*

## Fluidione, pentoxifylline Same trade name caused serious medication error; need to promote use of INNs

**France.** The French health-care products regulatory agency AFSSAPS is warning that having the same trade name for two different medicines can lead to serious medication errors. The Agency gives the example of a recent case that occurred in France: a 42 year-old male patient had been using fluidione (Previscan) since 2003 as an anticoagulant medication for atrial fibrillation. The patient forgot to carry his medication when he travelled to Spain in June 2005. There was no product by the name Previscan in Spain. The Spanish pharmacy then gave the patient pentoxifylline based on a reference that pentoxifylline is sold as Previscan in Argentina. On returning back to France on 27 June 2006 the patient switched back to his original French Previscan (fluidione) preparation. On 30 June 2006 the patient suffered a cardiovascular event with subsequent hemiplegia. The patient had to be hospitalized for three months. The patient has now recovered his mobility but has severe aphasia and ptosis that require surgery. The patient's wife discovered the mix-up only recently, and called the Marketing Authorization Holder (MAH), Procter and Gamble to notify them about the event.

AFSSAPS has informed the Spanish and Argentinean regulatory Agencies, the Argentinean Previscan (pentoxifylline) MAH and, the European Pharmacovigilance Working Party about the event. AFSSAPS has also warned health-care professionals and the public about the risks of potential medical errors that could occur when different drugs have the same trade name. AFSSAPS also advises that this is an important case for promoting the use of International Nonproprietary Names (INN) for medicines since an INN is a unique identifier for every medicinal product.

**Reference:**  
*Communication from Dr Carmen Kreft-Jais, Head, Pharmacovigilance Unit, AFSSAPS, 20 June 2007.*

### US FDA, EMEA and the European Commission: expanding the areas of cooperation

The US FDA, EMEA and the European Commission have agreed to expand the areas of cooperation under their confidential information sharing agreement. The parties agreed to include the areas of paediatrics and medicinal products for rare diseases (orphan drugs) in the agreement. In addition, scientific discussions have been widened to include extensions of therapeutic indications and risk management plans. Also, a 'Principles of Interaction' document was finalized, facilitating the timely exchange of information on scientific and ethical issues for paediatric drugs, and new areas for cooperation were discussed - notably medical devices and cosmetics.

**Reference:** [www.fda.gov](http://www.fda.gov)

**Paul-Ehrlich Institut (PEI): database of adverse reactions following vaccination**

The German Paul-Ehrlich Institut (PEI) has announced that it is providing a database containing detailed information on cases of suspected adverse reactions following vaccination. This initiative follows growing concern in many countries, including Germany, about real and alleged risks associated with vaccinations. The database is available via the PEI website. It will include data on reports submitted since January 2001 for the time being, but data starting from 1992 will be added later. The database will be updated 6-monthly.

**Reference:**  
*Reactions Weekly, No. 1158:2, 30 June 2007*

## Non-prescription cough and cold medicines

### Caution needed with use in children

**USA.** The US FDA is currently reviewing the safety and effectiveness of non-prescription cough and cold medicines use in children. The FDA wishes to determine whether the benefits from these products justify any potential risks associated with their use in children, especially in children under two years of age. Some of the serious adverse events reported with these products appear to be related to the amount given to the children. The US FDA has issued a Public Health Advisory to warn that an over-the-counter medicine can be harmful if more than the recommended amount is used,

if it is given too often, or if more than one cough and cold medicine containing the same active ingredient are being used. Parents are advised to carefully follow the directions for use on the product label. The Advisory lists a set of facts that parents need to know about using cold and cough products in children and include the following highlights:

- Do not use cough and cold products in children under two years of age unless given specific directions to do so by a health-care provider
- Too much medicine may lead to serious and life-threatening side effects, particularly in children aged two years and younger
- For liquid products, parents should use the measuring device (dropper, dosing cup or dosing spoon) that is packaged with each different medicine formulation and that is marked to deliver the recommended dose. A kitchen teaspoon or tablespoon is not an appropriate measuring device for giving medicines to children.
- If a measuring device is not included with the product, parents should purchase one at the pharmacy
- If a child's condition worsens or does not improve, stop using the product immediately and take the child to a health-care provider for evaluation.

**Reference:**  
*Public Health Advisory. U.S. Food and Drug Administration, 15 August 2007 ([www.fda.gov](http://www.fda.gov)).*

## Norethisterone Reports of decreased lactation

Health Canada has received 13 domestic reports of decreased puerperal lactation suspected of being associated with the use of

norethisterone between 1972 and 20 April 2007. Some reports noted that infants were not gaining weight or had lost weight. Norethisterone is a progestin-only oral contraceptive.

The reported cases involved postpartum women aged 22-35 years. Of the 13 cases, nine cases involved norethisterone treatment initiated less than six weeks after delivery; in three cases, norethisterone therapy was started less than six weeks after delivery. The reaction onset ranged between 3 to 16 days following the start of norethisterone therapy, as reported in nine cases. Following the withdrawal of norethisterone therapy, 10 women experienced increased puerperal lactation. Of these, three had used health products (domperidone, fenugreek and blessed thistle) to improve lactation.

*Reports in the WHO database for norethisterone (Micronor): Lactation Puerperal decreased 20*

**Reference:**  
*Canadian Adverse Reaction Newsletter Volume 17 (3):3 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).*

## Propofol Reports of chills, fevers, body aches

**USA.** The US FDA is warning health-care professionals about recent reports that several clusters of patients experienced chills, fever and body aches shortly after receiving propofol (Deprivan) for sedation or for general anaesthesia. All patients are reported to have recovered with no obvious sequelae. In general, patients who develop symptoms of acute febrile reactions shortly after propofol administration should be evaluated for bacterial sepsis. The FDA has confirmed that there was no evidence of bacterial sepsis in these patients. The FDA has also verified that the injection

lots were free from endotoxins and bacterial contamination. The FDA is working closely with the Centres for Disease Control and Prevention (CDCP) to investigate possible reasons for the patients' illnesses following propofol administration. In the meantime health-care professionals are requested to report similar observations in patients and to carefully follow the product handling and use instructions given in the propofol label.

*Reports in the WHO database:*

Fever	316
Pain	51
Rigors	7

**Reference:**

FDA Alert. U.S. Food and Drug Administration, 15 June 2007 ([www.fda.gov](http://www.fda.gov)).

## Rituximab

### Reports of progressive multifocal leukoencephalopathy (PML)

**Canada.** Rituximab (Rituxan) is a recombinant monoclonal antibody indicated for the treatment of B-cell non-Hodgkin's Lymphoma (NHL) and Rheumatoid Arthritis (RA). The efficacy and safety of rituximab in the treatment of autoimmune diseases other than RA has not been established. Hoffmann-La Roche Limited in consultation with Health Canada is warning that cases of fatal PML have been reported with the use of rituximab in certain autoimmune diseases including Systemic Lupus Erythematosus (SLE) and Vasculitis. The concerned patients had a history of prior or concurrent immunosuppressive therapy and were diagnosed with PML within 12 months of their last infusion of rituximab. PML has also been reported in patients with autoimmune disease not treated with rituximab. This makes it difficult to establish a

causal relationship between rituximab and PML. Hoffman La-Roche advises that physicians treating patients with autoimmune disease should consider PML in the differential diagnosis of patients reporting neurological symptoms. In patients who develop PML, rituximab should be discontinued, other concomitant immunosuppressants should be either reduced or discontinued and appropriate treatment should be considered for PML, although there are no known interventions to reliably prevent or treat PML.

**Reference:**

'Dear Health-care Professional' letter from Hoffman-La Roche, 8 August 2007 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).

## Salbutamol sulfate for injection

### Myocardial ischemia in pregnancy

**Canada.** GlaxoSmithKline (GSK), in consultation with Health Canada, warns that up to the end of April 2007 there have been 17 occurrences worldwide of events of myocardial ischaemia in pregnant women who received salbutamol sulfate solution for injection to delay premature labour. Eleven reports were serious and one was fatal. Where reported, 12 patients fully recovered without sequelae. The majority of the reports were associated with the use of parenteral formulations (Ventolin IM injection or Ventolin IV infusion solution), none involved the use of inhaled salbutamol formulations for bronchospasm. The observation of myocardial ischaemia in pregnant women following the administration of either beta-agonist as a class or salbutamol more specifically is well documented. Therefore caution should be used if

women are to receive intravenous salbutamol during premature labour. GSK recommends that, if the benefit of salbutamol sulfate for injection (Ventolin IM injection or Ventolin IV infusion) outweighs the risk in premature labour, fluid balance and cardiorespiratory function should be carefully monitored. If pulmonary edema or MI develops, treatment discontinuation should be considered. (Salbutamol is not indicated to stop or prevent premature labour in Canada).

**Reference:**

Advisories, Warnings & Recalls. Health Canada, 12 June 2007 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).

## How to classify drugs and measure drug consumption - a course in the ATC/DDD methodology

Marit Rønning  
Director, WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway

**A two-day course in the Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) methodology has been organized by the WHO Collaborating Centre for Drug Statistics Methodology in Oslo every year since 1995. The course provides basic knowledge and applications of the ATC/DDD methodology.**

### **WHO Collaborating Centre for Drug Statistics Methodology**

The Centre is situated at the Norwegian Institute of Public Health in Oslo and is responsible for the development and updating of the ATC/DDD system. New drugs are classified and DDDs are assigned by the Centre in cooperation with the WHO International Working Group for Drug Statistics Methodology. This Working Group includes international experts in the fields of clinical pharmacology and medicine, international public health experts, professionals dealing with drug regulatory issues and those involved in drug utilization research.

The staff of the WHO Centre in Norway have a long-standing experience in working with the ATC/DDD methodology and in the use of the system in drug consumption statistics. The Centre is also involved in the calculation of the national drug consumption statistics for Norway, this being the responsibility of the Norwegian Institute of Public Health. This is regarded as an optimal situation in the sense that the "caretakers" of the methodology are also users of the same methodology and therefore are fully aware of the implications of the technical decisions in practice.

### **The annual ATC/DDD course in Norway**

The course is open to all. However, basic knowledge in common medical terminology is recommended. The number of participants has varied from 20 to 45 in previous years and they come from health authorities, universities, research institutes, hospitals, pharmacies as well as from pharmaceutical industry. Normally, between 15 and 25 countries are represented. However, at least so far, around 80 % of the participants have come from European countries.

The course is interactive and includes lectures and working group sessions. The lectures cover the following topics:

- Background, overview and development of the ATC/DDD methodology
- Procedures for applications (ATC codes, DDDs and changes)
- The main principles for establishing new ATC codes and assigning DDDs
- ATC codes and DDDs for combinations
- Different applications of the ATC/DDD methodology
- ATC/DDD in drug consumption statistics

The working group sessions are important elements of the course. A wide range of ATC/DDD problems and points to consider related to the application of the methodology in drug consumption statistics are discussed. As a follow-up to the course, the participants are invited to share their experiences in the use of the ATC/DDD methodology.

At the latest ATC/DDD course the Chair of the WHO International Working Group for Drug Statistics Methodology presented his experiences in working with the Group and with the Centre. This was acknowledged as a valuable contribution to the course.

The course in Oslo is usually scheduled in June every year; course details and the registration form are posted on the Centre's website ([www.whocc.no](http://www.whocc.no)), in the month of November/December of the preceding year.

### **ATC/DDD courses in other countries and regions**

Over the years the Centre in Oslo has been invited to offer their course in other countries and regions. The initiative often comes from national or regional organizers who recognize the value of the ATC/DDD system and the need to educate professionals in the methodology. In these instances the local organizers

take care of the practical arrangements for the course, while the Centre's staff take care of the course content with its lectures and the working group exercises. ATC/DDD courses have been held in European and in non-European countries including Canada, Ecuador, Egypt, Japan and Morocco. Some of these have been regional courses with several countries represented at the course, others have been national courses.

### **Experiences and evaluation of the courses**

The ATC/DDD courses have received a very positive feedback from the participants, indicating a general need for training in the ATC/DDD methodology. The content of the courses have been developed over the years, mainly based on suggestions from participants at previous courses. An important basis for the success of the course is the combination of lectures and discussion of problems in smaller working groups. When the course is offered in Oslo, all senior advisers from the Centre are present at the course, assisting the groups. This gives participants the opportunity to interact individually with the Centre staff and to follow-up with key persons on supplementary issues/questions regarding the use of the methodology.

At the courses in other countries and regions, normally two representatives from the Centre are present to lecture and to give advice in the working groups. These courses are sometimes slightly different in content depending on the local knowledge and experience with the methodology. Offering national courses has been a good experience, both for the Centre and for the country in question. The advantage with national courses is that it is possible to educate a group of professionals who will work together in the area in the future. Besides, it is possible to focus on relevant examples and problems valid for the particular country. The regional courses with participants from several countries have also been received very well. Regional courses have the advantage of bringing together several countries that will benefit from the interaction, not only from the training, although the possibilities of dealing with particular problems in depth are somewhat limited.

## Sixteenth Meeting of the Global Advisory Committee on Vaccine Safety 12–13 June 2007, Geneva

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body established in 1999 to respond, independently from WHO, promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance, held its sixteenth meeting in Geneva, Switzerland, on 12-13 June 2007. Issues discussed were: vaccine safety monitoring; the safety of vaccine formulations; a mumps vaccine strain repository; the safety of BCG, human papillomavirus (HPV), rotavirus and influenza vaccines; and the safety of the meningococcal vaccine Menactra®.

### **Safety of HPV vaccines**

Current evidence of the safety of HPV vaccines is reassuring. As with the introduction of any new vaccine, it will be important to conduct surveillance to identify possible, rare, unexpected events, especially as good quality information on pre-vaccination rates of a variety of diseases is generally lacking in the target age group for HPV vaccination (9 to 26 years). In addition, careful surveillance for specific adverse events in or around pregnancy will be important as the target group for vaccination includes females of reproductive age.

### **Safety of rotavirus vaccines**

Data were presented on the Merck vaccine Rotateq™ and the GSK vaccine Rotarix™. GACVS concluded that with regard to intussusceptions, which had been identified as associated with a previous rotavirus vaccine, the data, particularly those from developed countries, are reassuring. It was noted, however, that the present data relate for the most part to vaccines administered to young children at the recommended age. Intussusceptions should be monitored in developing countries as rotavirus vaccines are introduced, especially as infants are likely to present for their first dose of vaccine at slightly older ages, on average, than is the case in developed countries.

Information was also presented on rare cases of Kawasaki disease observed following rotavirus vaccination. While the evidence is at best a hint of a signal, the data do not yet permit a full evaluation of a possible risk. There is a need for careful assessment of Kawasaki disease in the existing data and to ensure that ongoing and future studies incorporate surveillance for Kawasaki disease following vaccination.

### **Influenza vaccines**

Among other issues discussed, a brief description of allergic events occurring after administration of Grippol, a polyoxidonium adjuvanted split influenza vaccine produced in the Russian Federation, was presented. There is a paucity of information regarding these events and WHO has not been able to secure additional information on the investigation. As such, it is unclear if events reported in the media were compatible with expected rates of allergic reactions or represented an increase, and possibly some manufacturing problems. GACVS nevertheless recommends that countries using this vaccine put in place a surveillance system for the upcoming season so that its safety profile can be better characterized. Improved information sharing regarding the safety profile of influenza vaccines is critical for pandemic influenza preparedness.

*The report of the meeting was published in the WHO Weekly Epidemiological Record on 20 July 2007. Both this report and additional material on specific topics have been posted on the GACVS web site at [http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)*