WHO Drug Information

UPPSALA REPORTS 38

UPPSALA REPORTS July 2007

For everyone concerned with the issues of pharmacovigilance

Carl von Linné tercentenary

New member and associates

Educational initiatives

WHO Drug Dictionary training news

Buenos Aires WHO meeting preview

DIRECTOR'S MESSAGE

Ralph Edwards
Director
the Uppsala Monitoring Centre

My last message has resulted in some interest.

- The article referred to in my message, on the possible association between ALS and statins, has been published in a much expanded and improved form in 'Drug Safety': thank you, ADIS Press, for that.
- One major medical journal has approached me and is interested in finding a format for signals based on series of patients.
- SCRIP picked up the issue and produced a splendid, balanced piece on the issue which is summarised in this edition of UR.
- Perhaps most surprisingly the Wall Street Journal approached me over the issue and I have had extensive discussions with one of their reporters. She found the topic interesting, and has written a nuanced article on the difficulties of deciding what one does with an early signal [1]. It was a challenge talking to her, particularly to put over the balance of considering a serious medical condition, the potential public health risk, and limited information with tentative causality.

That it was right to publish the signal will be for history to decide, and I certainly hope there will be no drug scare. In support of publication, though, I wish to refer readers to a recent BMJ editorial on Rosiglitazone and cardiaovascular disorders [2]. The editorial, as often happens, declares that, 'Postmarketing surveillance, or pharmacovigilance, remains the weakest link in the regulatory process on both sides of the Atlantic', and that individual case safety reports are '...one of the weakest forms of epidemiological evidence, that would be insensitive to an increase in common events like myocardial infarcts in diabetics'. Actually, the possible associations with cardiac failure, cardiomegaly, myocardial ischaemia & infarction and angina pectoris were found in the WHO Database of ICSRs (Vigibase) and available to all national authorities from 2001 and were signalled after clinical review in 2003 (Signal: November, 2003). *The system did not at all fail: it generated the hypothesis early, and reported it for 3 thiazolidinediones.* Moreover the UK SPC on-line (November, 2003) also comments on the high frequency of heart failure in double-blind studies on rosiglitazone.

So we seem to be in the paradoxical situation of not being able to have important signals published, but to be told repeatedly that the global individual case safety reporting system does not work. We also face public and general health professional concerns that information is suppressed.

All those involved in drug safety do their work with minimal resources, and I think it is fair to say that the full scrutiny of every potential signal would not be cost effective. What we all try to do is to use our collective skills and experience to decide what to take forward and prioritise. None of us gets it right every time. Algorithms, such as Waller et al [3] describe, are useful, but I doubt if they can replace the need for wisdom and value judgements about what safety information will be useful to health professionals and what level of confidence in a signal is needed before further action, particularly publication.

References:

1. Johnson, A. http://online.wsj.com/article/SB118342971456956235.html
2. Kazi D. Rosiglitazone and implications for pharmacovigilance. BMJ 2007; 334 :1233-4.
3. Waller P, Heeley E, Moseley J. Impact analysis of signals detected from spontaneous adverse drug reaction reporting data. Drug Saf. 2005;28(10):843-50

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Intense learning

The 2007 UMC pharmacovigilance course took place in May with participants from all over the world.

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Carl von Linné

The man who led the way in classification in the natural sciences was born 300 years ago. We look at his life and legacy.

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VigiFlow software updated

Several technical updates are reported in this issue, including VigiFlow 3.2, use of MedDRA in the WHO database and new report inputting processes.

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New degrees

Two researchers working in *the* UMC's data mining team (including Niklas Norén, pictured) recently gained their higher degrees for studies involving the WHO ADR database.

the UPPSALA MONITORING CENTRE

The Uppsala Monitoring Centre (*the* UMC) is the field-name of the WHO Collaborating Centre for International Drug Monitoring, responsible for the management of the WHO Programme for International Drug Monitoring.

An independent centre of scientific excellence, *the* UMC offers products and services, derived from the WHO database of Adverse Drug Reactions (ADRs) reported from member countries of the WHO Programme.

With an independent and global perspective on drug safety, *the* UMC provides resources for regulatory agencies, health professionals, researchers and the pharmaceutical industry.

The UMC's important worldwide work is financed solely by the organisation itself, without support from WHO, the Swedish Government, member countries of the WHO Programme or any grant-making body.

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New member and associates

Sten Olsson reports

While UMC staff were busy preparing and leading the biennial pharmacovigilance training course in Uppsala, there have been positive developments over the last quarter in the WHO Programme for International Drug Monitoring. Three African countries have become Associate members of the Programme, while a new full member joined.

Uganda

Uganda submitted the necessary batch of ADR case reports (through VigiFlow) which fulfilled our requirements. Uganda has now become member country 83 of the Programme. Head of the Uganda centre is Helen Byomire Ndagije (who was one of the participants on our course this year). A full description of the Ugandan centre will follow, but the contact details are:

Mrs Helen Byomire-Ndagije
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National Drug Authority
Plot 46/48 Lumumba Avenue
PO Box 23096
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Uganda
Phone : +256 (41) 347391/2
e-mail : hbyomire@nda.or.ug www.nda.or.ug

Cameroon, Togo, Benin

In April Cameroon wrote to WHO to request admittance to the WHO Programme. This was followed in May by Togo and Benin.

Cameroon details:

Dr Emilienne Yissibi Pola
Chef de Service
Homologation et Pharmacovigilance
Direction de la Pharmacie et du Médicament
Ministère de la Santé Publique
BP 233 YAOUNDE
Cameroon
e-mail: pharmacovigilance_cam@yahoo.fr

The contact person for Togo is:

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Direction des Pharmacies, Laboratoires et Equipements Techniques
Bp 336
Lomé
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e-mail: elhaidinam@hotmail.com

The contact for Benin is:

Dr Marie-Agnès Agboton
MS/PNLP
08, BP 0028 Tri postal
Cotonou
Bénin
e-mail: agboton_zoumenou@yahoo.fr

Representatives of Cameroon, Bénin and Togo attended the Moroccan pharmacovigilance course for French-speaking African countries last February (see UR37).

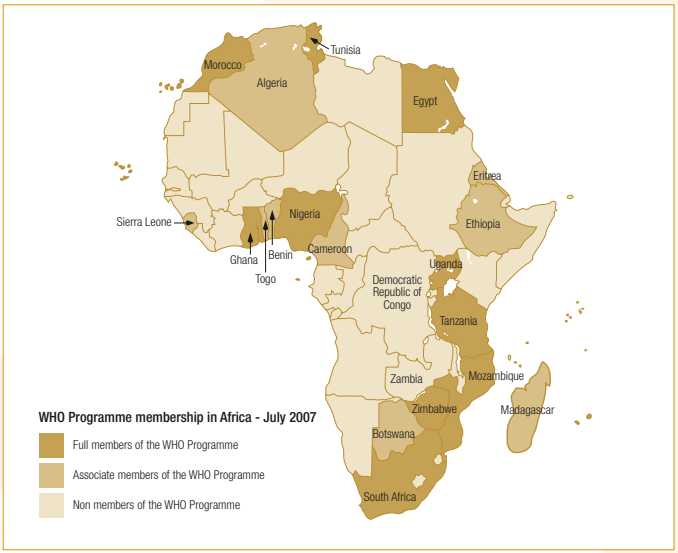
Another Associate in Europe

Finally, just as we were going to press, an application was received from the Minister of Health, Housing and Welfare in the Principality of Andorra, a land-locked Pyrenean country between Spain and France, with a population of 69,000.

Responsible for the pharmacovigilance centre is:

Cristina Vilanova Serrano
Department of Pharmacy, Products and Healthcare Centres
Avda Princep Benlloch, 30
AD500
Andorra la Vella
Andorra
e-mail: c.vilanova@andorra.ad

Cristina Vilanova visited *the* UMC briefly in May 2006; Andorra will be the 19th Associate Member country in the Programme.



Full member countries in Africa (date joined):

Egypt (2001)
Morocco (1992)
Nigeria (2004)
Tunisia (1993)
United Republic of Tanzania (1993)
Ghana (2001)
Mozambique (2005)
South Africa (1992)
Uganda (2007)
Zimbabwe (1998)

Associate member countries:

Algeria
Botswana
Democratic Republic of Congo
Ethiopia
Sierra Leone
Zambia
Bénin
Cameroon
Eritrea
Madagascar
Togo

UNICEF Infant Studies

another front opens in the battle for drug safety

UNICEF is pilot implementing IPTi (Intermittent Preventive Treatment in Infants) against malaria in six African countries – where the pharmacovigilance systems are relatively new or nearly absent. With an expected uptake of about 500,000 doses of Sulfadoxine-Pyrimethamine (SP) across the 6 countries, it is important to have a robust pharmacovigilance system for detection of adverse events.

Pharmacovigilance and IPTi

The need for making pharmacovigilance an integral part of the UNICEF IPTi studies has been recognised. In three of the six implementing countries (Benin, Ghana, Madagascar, Malawi, Mali and Senegal), the national Ethics Committees specifically raised concerns on safety and demanded urgent and demonstrable safety actions and strengthening of pharmacovigilance to accompany the pilot implementation of IPTi. The administration of SP for IPTi at the same time as administration of routine childhood vaccines poses further difficulties in assigning causality to any product-related adverse events and requires appreciation of the likely contribution of the various products.

Structure and methods

Ghana is co-ordinating the pharmacovigilance studies for all six countries, offering support in areas of training, data management, causality assessment and communication, in a collaboration between UNICEF and the University of Ghana Medical School. Both passive and active drug safety monitoring strategies are employed.

Objectives

The PV network aims to:

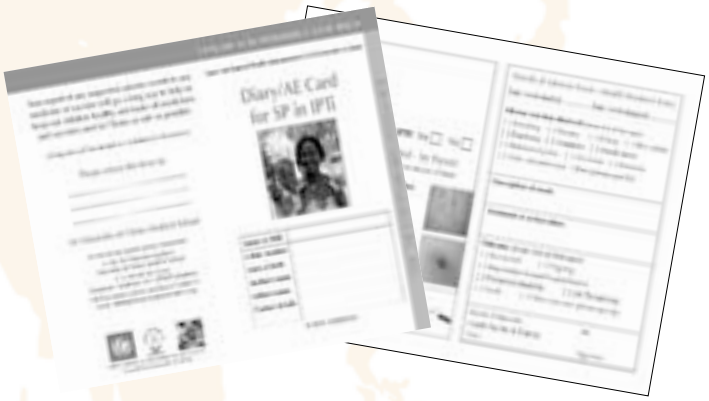
1. document, investigate and assign causality to all adverse events following administration of SP for IPTi
2. strengthen the existing national pharmacovigilance systems.

Passive monitoring involves:

- situational analysis within each district on the operation of the existing spontaneous system
- training of healthcare workers, EPI staff and parents on the pharmacovigilance system with encouragement to report all unwanted/adverse events
- reporting by parents/carers, health workers and EPI staff. All parents of infants given SP for IPTi are given a reporting card with details on what to do and who to contact in case of adverse events
- reporting of all adverse events regardless of severity to create a culture of reporting and ensure that no events are missed
- investigation of all serious events and any severe dermatological reaction
- acceptability assessment of the pharmacovigilance system.

Active 'cohort event monitoring' is being carried out in Ghana:

- Children in selected districts are followed-up regardless of whether they have any adverse event or not
- Each parent is given a diary/adverse event card after each administration of SP for IPTi. The card is used to record any occurring adverse event.
- Each child is contacted 7-10 days after administration of SP for IPTi by trained pharmacovigilance workers and/or community based health volunteers
- The expected cohort is a minimum of 10,000 patient events (doses of SP) during a period of six months. This will permit identification of adverse events happening at a frequency of 1 in 3,000.



The Global IPTi network has established a Consortium Safety Panel (CSP) consisting of experts in pharmacovigilance, statistics, clinical medicine, epidemiology and ethics, to overview the safety data being generated from IPTi studies. This is a major advantage of operating as a Consortium, as robust safety data is likely to be greatly valued in policy discussions. The CSP members are:

Sir Alasdair Breckenridge, Chairman of the Medicines and Healthcare Products Regulatory Agency (MHRA), *UK* (Chair)
Julia Critchley, University of Newcastle, *UK*
Alex Dodoo, University of Ghana Medical School, *Ghana*
Zul Premji, Muhimbili University, Dar es Salaam, *United Republic of Tanzania*
Esperanza Sevene, Eduardo Mondlane University, Maputo, *Mozambique*
Rachida Soulaymani, Director of the National Pharmacovigilance Centre, Rabat, *Morocco*
Peter Winstanley, Director of the Wellcome Trust Tropical Centre, University of Liverpool, *UK*

Remit of dual approach

The pharmacovigilance programme – both active and passive – being implemented in the UNICEF IPTi implementation studies will allow identification of bottlenecks and obstacles to collection of safety data in resource-constrained environments. It is essentially a collection of ADRs to drugs and adverse events following immunization (AEFI) and will allow best practices to be documented to improve safety monitoring in the countries involved.

For more information see: www.ipti-malaria.org

UMC joins the RaPID™ initiative

Rapid Pharmacovigilance Implementation in Developing countries

Implementing Drug Safety Monitoring in 90 days

Paul Lalvani and Sten Olsson

This sounds like a tall order but we, the partners involved (see below), are convinced we can do it. It requires a new approach to pharmacovigilance and new resources which we will try hard to get.

Using Public Health Programmes

The analysis underpinning the RaPID initiative is based on the massive scaling-up of drug treatment of HIV/AIDS, malaria and tuberculosis that major donors (Global Fund, PEPFAR, PMI, Gates Foundation, Clinton Foundation etc) are currently undertaking through Public Health Programmes in countries where only rudimentary systems for pharmacovigilance exist, if at all. Many of the medicines employed by the Public Health Programmes are new and/or have safety concerns associated with them. Their adverse reaction profiles are often developed only on the basis on experience from industrialized countries. By making such new and insufficiently studied medicines available to new populations on a massive scale in settings with little or no drug monitoring in place the donors are exposing both patients and donors to unnecessary risks.

Training teams

The new initiative emphasizes the benefits of applying pharmacovigilance, which can significantly improve the impact of donor-supported public health programs, and provides a mechanism to implement this activity in less than 100 days. The concept includes the establishment and training of a pharmacovigilance field force that will actively assemble case information from the treatment centres of the Public Health Programmes. RaPID will provide staff to enter this data into country-specific databases, using the VigiFlow software developed by *the* UMC. A team of signal reviewers will be trained to analyse the collected case information and to highlight any indication of new patient safety concerns. Such information will regularly be provided to Public Health Programme managers and regulatory authorities in each country in which the system is operating and to the international community when considered relevant.

World-wide partners

In addition to *the* UMC the RaPID consortium presently consists of the following partners:

- The Ecumenical Pharmaceutical Network, an independent, apolitical non-profit Christian organization with 80 pan-African members providing healthcare in 31 countries
- All India Institute of Medical Sciences, AIIMS, a leading centre for research, education and health care delivery in New Delhi, India. AIIMS is one of two zonal centres for pharmaco-vigilance in India
- O3i™, a New York-based non-profit consulting organization
- Indian Institute of Health Management Research in Jaipur, India. The institute undertakes training, research and consultancy in health management.

The UMC will have a key role in the consortium by providing a number of services:

- Training of the field force regarding the collection of relevant patient and case details
- Access to the VigiFlow software for management of individual case safety reports
- Training for VigiFlow users
- Provide tools for data analysis
- Training of staff in case assessment, signal analysis and benefit/harm evaluation
- Communicating results to relevant national authorities and international partners.

the UMC has a long history in providing development support for national pharmacovigilance programmes. This initiative is a new approach for swiftly building capacity for pharmacovigilance activities in developing countries, to create data sources as a basis for regulatory decision-making and to promote collaboration between Public Health Programmes and national pharmacovigilance systems.

Further information about the initiative may be gained from www.rapidpharmacovigilance.org. If you are interested in the approach please contact Sten Olsson at *the* UMC (sten.olsson@who-umc.org) or the Executive Director of the RaPID™ consortium, Paul Lalvani (paul.lalvani@rapidpharmacovigiliance.org, paullalvani@yahoo.com)

Plans for annual meeting in Argentina

The preliminary programme for the 2007 Annual Meeting of the WHO Programme for International Drug Monitoring, in Buenos Aires, Argentina has been circulated to national centres.

The Administración Nacional de Medicamentos, Alimentos y Tecnologia Médica (ANMAT – the national agency in Argentina) is hosting the 30th Annual Meeting of the WHO Programme. Dr Inés Bignone, Head of ANMAT's Pharmacovigilance Department says "We welcome all the delegates from around the world to our country and very much hope that Buenos Aires will be a great place for colleagues to work on developing the WHO Programme, but also that they can get to know our city and the hospitality of the people".

These meetings are an important forum for members of national pharmacovigilance centres to come together and discuss topical matters of high significance in a congenial environment. Over the past thirty years the network of pharmacovigilance centres has grown immensely and the annual meetings have become a noteworthy event for the discussion of safety of medicines.

There will be a tutorial for all those who are newcomers to the WHO Programme on Wednesday 10th October at 14.00, with an overview of the Programme and the work of *the* UMC, practical advice and information, and the opportunity to ask questions in the group. The meeting itself starts on Thursday 11th October.

Programme

After the Official Opening on Thursday morning, there will be reports from WHO Headquarters and *the* Uppsala Monitoring Centre, and feedback from the 2006 meeting in Liège. A talk about 'Global awareness of pharmacovigilance' will be followed by working groups looking at:

- Opening the WHO database - which E2B fields to be open to the public?
- Access to 'Signal' document
- How to get information to patients
- Identifying risks in special populations - women and children.

On Friday, sessions include:

- Pharmacovigilance methods in public health programmes
- Cohort Event Monitoring (CEM) in Africa
- Surveillance strategies in India, particularly for visceral Leishmaniasis
- Passive stimulated reporting strategies in South Africa.

As well as updates on:

- Patient safety pilot project
- Preparedness for pandemic 'flu
- Initiatives in vaccine pharmacovigilance
- Practical consequences of the WHO-ART–MedDRA bridge.

There will also be discussion groups on:

- Patient safety
- Initiatives in vaccine pharmacovigilance
- Complementing spontaneous reporting with other methodologies e.g. CEM and passive stimulated reporting.

Saturday morning has a presentation of drug safety in Argentina, feedback from working groups and the announcement of the host for the 2008 Annual Meeting. As always, Drug Problems of Current Interest will be prominent throughout the agenda.

There will be opportunities for delegates to do some sightseeing on Sunday 14th October.

A view over the Argentinean capital.

Getting there

Most delegates will arrive at the Ministro Pistarini International Airport, (simply called 'Ezeiza') which has flights from all over the world. Aeroparque Jorge Newbery airport serves neighbouring countries and domestic traffic. The Buenos Aires Metro (known as 'el subte') has five lines, 80 stations, and 46 km of track.

The Argentine currency is the peso (using the $ symbol). There are $ 100, $ 50, $ 20, $ 10, $ 5 and $ 2 notes, and a variety of coins. Banks and 'casas de cambio' (currency exchange offices), exchange foreign currency; shops accept many credit cards and US dollars.

A guide in your language

A series of practical guides in Spanish, Portuguese, Russian, French, Mandarin, German, Italian, English, Japanese and Arabic are available in pdf format from the City of Buenos Aires website. See http://www.bue.gov.ar/informacion/?menu_id=121&tinfo=guias (the home page is http://www.bue.gov.ar/)

Preparing the next wave of pharmacovigilantes

The 2007 UMC training course

Despite having taken place every other year since 1993, *the* UMC's two-week course is still very much in demand. Programmes for spontaneous adverse reaction reporting are established in an increasing number of countries around the world but there are always new staff and new member countries eager to soak up two weeks of solid learning in ADR monitoring and related topics. The course can also act to reinvigorate ADR systems which have been in the doldrums.

Course participants and faculty on the steps of the Carolina Rediviva library in Uppsala.

This May, 24 participants from an equal number of countries attended the first 8-day Module focusing on various aspects of spontaneous adverse reaction reporting. Most of these then stayed on, joined by other participants, for one of two second module options, either a) Introduction to pharmacoepidemiology, or b) Effective Communications in pharmacovigilance. *See box for full list of participants.*

Experienced staff from *the* UMC were joined this year on the teaching faculty by experts from the Swedish Medical Products Agency, the University of Utrecht, Lareb, Bayer Schering Pharma and WHO Headquarters.

The course combined lectures and discussion, with small group work and 'hands-on' practice in the WHO database, to give the participants a chance to try entering and searching data.

The response from the evaluation forms was overwhelmingly positive, with the relaxed environment much appreciated. Many students requested more 'practical' work - using the WHO database, and some found the workload quite heavy in terms of digesting the day's learning. There were some problems in participants receiving information provided before the course, with others asking for more pre-reading to prepare themselves.

Over the two weeks the international participants not only had a chance to forge new friendships with colleagues but also to see a little of Uppsala and, on a day trip, the capital of Sweden, Stockholm. *the* UMC course coincided with the peak of the 300-year anniversary celebration of the main scientific celebrity of Uppsala, Carl Linneus. It was the cause of some excitement that Uppsala, during this period, was visited both by the Japanese Emperor and former UN secretary general Kofi Annan.

List of participants

Rudolf Schranz *Austria*
Christos Petrou *Cyprus*
Diego Macias Saint-Gerons *Spain*
Maria Sainz Gil *Spain*
Sasa Zezelic *Croatia*
Nikola Jelkic *Serbia*
Jenny Roed *Norway*
Maryam Hinds *Barbados*
Henry Luma *Cameroon*
Jean Nkanza *Canada*
Le Yang *China*
José Terán *Ecuador*
Assegid Tassew Mengistu *Ethiopia*
Nartekour Nartey *Ghana*
Suparna Chatterjee *India*
Siti Asfijah Abdoellah *Indonesia*
Jayesh Pandit *Kenya*
Ja-Young Kim *Republic of Korea*
Norleen Mohamed Ali *Malaysia*
Alejandra Rosete *Mexico*
Johannes Gaeseb *Namibia*
Adeline Osakwe *Nigeria*
Anna Gratsianskaya *Russian Federation*
Evans Sagwa *Rwanda*
Ghazi Saleh M Saeed *Saudi Arabia*
Adena Lim *Singapore*
Khalid Hamid Mohamed *Sudan*
Naomi Jessurun *Suriname*
Shija Joseph Shija *United Republic of Tanzania*
Helen Byomire-Ndagije *Uganda*

New Western Pacific Chapter of ISoP

At the International Society of Pharmacovigilance (ISoP) annual meeting in Liège in October 2006, a group from New Zealand, Philippines and Australia discussed the possibility of establishing a regional Chapter of ISoP. Chapters are locally established sub-groups of the Society which are intended to actively address the needs arising from a range of pharmacovigilance activities in their respective countries. One important aim is to enable ISoP members to be personally involved in the future of pharmacovigilance in their region.

Following on from these initial discussions, it was decided that the new Chapter of ISoP should include members in the countries in the WHO Western Pacific region (as shown in Table 1).

ISoP members in Taiwan and Thailand have also been included in the Western Pacific Chapter. There are currently no other ISoP members in countries in the South East Asia WHO region.

The proposals for the new Western Pacific Chapter have now been approved by the ISoP Executive Committee. There has also been a very positive response from ISoP members in the Western Pacific region (who have all been sent the proposals) with many people volunteering to assist in the development of the new Chapter.

The first Coordinator of the Western Pacific Chapter will be Dr Mira Harrison-Woolrych (pictured) who is the Director of the New Zealand Intensive Medicines Monitoring Programme (IMMP). Dr Suzette Lazo – former President of the Philippine Society of Experimental and Clinical Pharmacology and a member of the ISoP committee on elections 2006 - has agreed to act as Secretary of the new Chapter. Drs Harrison-Woolrych and Lazo are very enthusiastic about the formation of the new Chapter and are encouraging all those with a keen interest in pharmacovigilance in the Western Pacific region to consider joining ISoP (www.isoponline.org) and participate in activities in this region.

Table 1: Countries included in the WHO Western Pacific Region

* Countries with current ISoP members

American Samoa	Nauru
* Australia	New Caledonia
Brunei Darussalam	* New Zealand
Cambodia	Niue
* China	Northern Mariana Islands
Cook Islands	Palau
Fiji	Papua New Guinea
French Polynesia	* Philippines
Guam	Pitcairn Islands
Hong Kong (China)	Samoa
* Japan	Singapore
Kiribati	Solomon Islands
* Korea, Republic of	Tokelau
Lao People's Democratic Republic	Tonga
Macao (China)	Tuvalu
* Malaysia	Vanuatu
Marshall Islands	Viet Nam
Micronesia, Federated States of	Wallis and Futuna

Mira Harrison-Woolrych and a map of the area for the new ISoP Chapter.

The Western Pacific Chapter will be launched at the annual ISoP meeting in Bournemouth, UK in October 2007 (www.isop2007.org). There will be a specific session about pharmacovigilance in the Western Pacific region and those interested are encouraged to attend. ISoP are also planning a pharmacovigilance course in Bangkok in March 2008. The final details should be available at the ISoP annual meeting in Bournemouth.

Anyone interested in joining the Western Pacific Chapter is invited to contact either:

Mira Harrison-Woolrych (Chapter Coordinator) at:
Mira.harrison-woolrych@otago.ac.nz or
Sophie Spence (ISoP administration) at:
administration@isoponline.org

Oriental Medicine in Japan

Marie Lindquist visits Keio University

After the WHO-FIC meeting in Odawara (see page 14), the opportunity arose to visit the traditional medicine department of Dr Watanabe, at Keio University in Tokyo. We were looked after by Dr Kenji Shuto, the Japanese ICD Centre Head, travelling by the 'bullet' train Shinkansen to the gigantic Tokyo station, and by underground to Keio University. There we were met by Dr Watanabe, who had come straight from a meeting in London to the Sunday dinner of the WHO-FIC, attended the whole FIC meeting, and gone straight back to see 52 patients that morning!

We were taken to the Vice Dean's office for an informal and friendly welcome, followed by a photographic session. After this, we were escorted by Dr Watanabe to the hospital laboratory, with a large number of sophisticated DNA sequencers and other machines. These are used to analyse both 'normal' samples, as well as the ingredients of traditional medicines.

The last stop on our hospital visit was in Dr Watanabe's office where we followed with interest a repeat of a presentation Dr Watanabe gave the week before in London, about the principles and practice of Kampo medicine in Japan. A key feature of the medical practice in Japan is that most doctors (around 70%) use both western medicine and Kampo medicine. Kampo medicine is to a very high extent standardised; the Kampo products are made and sold by around 10 major pharmaceutical companies in Japan which all use (combinations of) standardised ingredients defined in the Japanese Pharmacopoeia. One of the dilemmas of traditional medicine is the lack of 'evidence' that it works, and the difficulty to produce scientifically acceptable proof (as we know it). Since the philosophy of Kampo, and other traditional medicine in Asia, builds on individual diagnosis and treatment, with a mixture of compounds tailored for each person, the notion of a clinical trial as we know it, with one target disease, and one drug to treat it, simply could not be done.

However, Dr Watanabe and his team have been able to produce some evidence as to the efficacy of Kampo medicine. He showed figures from a study of the use of a Kampo formula in patients who had undergone surgery for bowel cancer. The Kampo drug was given to stop adhesions of the gut, which is a complication that could happen after the surgery. The data showed that the hospital stay was substantially shortened for those patients who had been treated.

Another idea of Dr Watanabe's was to use data mining of patient records to study the effects of the use of Kampo medicine. His enthusiasm was high when I told him what *the* UMC are doing in data mining, and we agreed to exchange information and consider how to pursue collaboration. The interest in Asian medicine is growing in the western world - maybe we can learn from each other, and improve medical care everywhere.

Kampo medicine is the Japanese study and adaptation of Traditional Chinese medicine. The basic works of Chinese medicine came to Japan between the 7th and 9th centuries. Since then, the Japanese have created their own unique herbal medical system and diagnosis.

Early drug problems

how to alert?

The issue of difficulties for *the* UMC getting signals, or hypotheses, published in major journals was highlighted in Uppsala Reports 37 in April. Ralph Edwards wrote "How long must we continue before we accept that there is no 100% certainty and that we need to weigh all evidence, and the context in which it was obtained, against the kind of decisions we have to make, and the seriousness of their consequences to patients' health."

Scrip magazine took up the arguments (Issue no 3263/64; May 30th – June 1st 2007) and interviewed both Ralph and Rosie Stather, the editor of *Drug Safety* journal. Scrip also spoke to senior editorial staff of *The Lancet* and the *BMJ* about their policies for accepting such papers.

Pharmacovigilance in Nepal is growing

Anna Celén writes

On a sunny morning last April I boarded a flight to Nepal. The main purpose of my trip was to experience work at a Nepalese pharmacy, but I also visited the Department of Drug Administration (DDA) in Kathmandu and the Drug Information and Pharmacovigilance Centre (DIPC) at Manipal Teaching Hospital in the beautiful city Pokhara, situated at the foot of the snow-capped Himalayas.

The audience for Anna's talk at the DDA.

The pharmacist Ganesh Maharjan, owner of Xeno Pharmacy in Kathmandu, explained the routines of his pharmacy as well as the general drug situation in Nepal. It was a valuable experience for me and I'm very grateful for his hospitality.

I was invited to make presentations about pharmacovigilance at DDA and Manipal Teaching Hospital. The aim of the presentations was to emphasise the importance of pharmacovigilance and encourage health professionals to report ADRs. The audiences consisted of doctors, nurses, pharmacists and medical students. Since the pharmacovigilance programme of Nepal was established quite recently, it's a challenge for the staff at DDA and DIPC to create awareness of the need for ADR reporting.

The lecture theatre in Manipal.

At DDA, Pradeep Gyawali and Professor Kumod Kumar Kafle from Tribhuvan University Teaching Hospital (TUTH) presented an ADR study performed at their hospital. They showed that dermatological reactions caused by antibiotics accounted for the majority of ADRs in the study. The Director of DDA, Bhupendra Bahadur Thapa, made a request to include TUTH as a regional centre in the pharmacovigilance programme and Professor Kafle agreed to this.

I had several fruitful discussions with the staff at DDA, especially Director Thapa, Gajendra Bahadur Bhuju, Santosh KC and Joshna Shrestha. Some topics of interest were the future expansion of the pharmacovigilance programme of Nepal, ADR reporting in general and current problems with reporting. I also provided hands-on VigiFlow and Vigisearch training.

While visiting Manipal Hospital I had the privilege to meet the Director of the hospital, Dr S K Dham and the Medical Superintendent Dr S P Kapoor, as well as the staff at DIPC. Palaian Subish enthusiastically presented the activities at the centre and I was impressed by their high ambition and creativity. I also had the chance to discuss pharmacovigilance with Dr Pranaya Mishra, Kadir Alam and Dinesh Kumar Upadhyay. Eighteen pharmacists are employed at the hospital and about half of them are involved with pharmacovigilance. So far, 180 reports have been collected at the centre.

During my stay in Nepal I was also invited to the following hospitals in Kathmandu: TUTH, Shahid Gangalal National Heart Centre, Manmohan Memorial Hospital, Kathmandu Model Hospital and Patan Hospital. I was received by dedicated pharmacists who were all interested in joining the pharmacovigilance programme as regional centres as soon as possible, even though lack of resources is a problem.

I would like to express my sincere gratitude towards all the people in Nepal who made me feel very welcome. I hope that I will have the opportunity to visit again someday and I'm confident that there will be major improvements in the pharmacovigilance programme of Nepal in the near future.

Linné – life and achievements

The tercentenary celebrations for the birth of Swedish botanist and physician Carl Linnaeus (1707-1778) have been celebrated around the world but nowhere more so than in his home city, Uppsala.

His work may be somewhat obscure to the average citizen of the world, but Linnaeus is famous as the father of taxonomy, the science of classification of living things. He set himself the remarkable task of describing the entire natural world by assigning each plant and animal a two-part name. This system of classifying living organisms became the international standard.

Carl von Linné – or Linnaeus – developed the revolutionary system of classification, or taxonomy known as the *Systema Naturae*, over years of careful observation. His famous book *Systema Naturae* classified 4,400 species of animals and 7,700 species of plants.

Linne's signature and Linnaea borealis L. on a poster by Sharon Stevenson for celebratory events at the Gustavus Adolphus College in Minnesota, USA. The image of the flower is by Anders Björling, son of the famous Swedish opera singer Jussi Björling. He took it last summer in Sweden on a trek to follow Linnaeus's path with Scandinavian Studies Professor Roland Thorstensson, like Anders a native of Sweden.

Linnaeus is also credited for distinguishing humans as *Homo sapiens* and as primates in the class of mammals. As a result of Linnaeus's work scientists of all countries were given a standardised set of names of all living things.

Swedish currency.

Carl Linnaeus was not only a scientist, botanist, zoologist and geologist; he was also a skilled doctor, and a philosopher. The Linnaean era is characterised by an ambition to catalogue, organise and give names to the whole natural world. Linnaeus attracted many disciples, and he has left a lasting impression in many locations.

Born on 23rd May 1707 in Råshult in the south of Sweden, Carl Linnaeus is credited with creating order out of chaos - the chaos of naming and identifying plants. Before Linnaeus, no system existed for giving workable, reliable names to plants, and thus no global capability for scientists and others who studied plants to communicate about them.

Such is his scientific renown, there are places on the Moon named after him. His face appears on the Swedish 100 kronor bank note, and an era of scientific history bears his name. But Carl Linnaeus is best known for creating the system of classifying living organisms that became the international standard.

The Emperor of Japan walks from Uppsala cathedral to the main university building followed by the Empress and the Queen of Sweden.

300 planters (replicas of the planters Linné himself used) and a long path of grass turfs were placed along a central street in Uppsala during the festivities.

Uppsala 300 celebrations

The celebrations in Uppsala included activities throughout the week of his birthday all over the city, in the cathedral, at the university, in the Botanical Gardens, and at Linné's Hammarby, his home in the country 15 kilometres outside the city.

On 20th May the inauguration of the anniversary week took place at the Uppsala Botanical Gardens, including the opening of the newly refurbished Linnéanum, an information centre and a new exhibition about Linnaeus.

A service of remembrance took place in Uppsala Cathedral on 23rd May, with guests of honour, including the Swedish King and Queen with Crown Princess Victoria, and the Emperor and Empress of Japan.

From 19th to 27th May, the whole of Uppsala was in festive mood with a Flower Day, activities for children, concerts, exhibitions, services at several churches and in the open air. Locations associated with Linnaeus held open days: the Linnaeus Garden, Linné's Hammarby (which visitors to *the* UMC pass in the bus from the airport), Linné's Sävja (another home near the city), and the Botanical Gardens by the castle. The week culminated in the promulgation of honorary doctorates to eminent scientists from all over the world at the university, all nominated in memory of Linnaeus, among them Kofi Anan former Secretary General of the United Nations, James Watson, Noam Chomsky and David Attenborough (see http://info.uu.se/press.nsf/pm/uppsala.universitys.id0AC.html for the full list).

A new tulip bulb was created for the Linné celebrations.

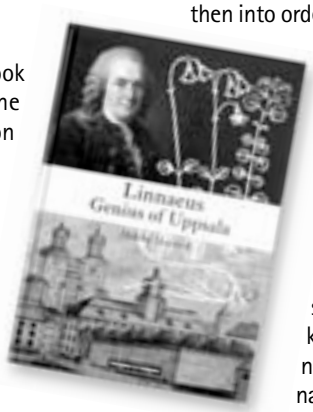
Linné's importance for the UMC and for drug safety

Linné's language is international, used by those heading to the nursery to purchase an Aloe vera L. (named by Linnaeus) as well as by researchers around the world working to produce new medicines from plants.

Before Linnaeus, scientific names for plants and animals were confusing and failed to convey relationships between them. However, under his system for plant taxonomy the name for a type of rose became simply *Rosa canina L.*, which replaced several confusing long, descriptive Latin phrases that varied from author to author, such as *Rosa sylvestris inodora seu canin* or *Rosa ciliato-sepala.*

To scientists and gardeners, the simple mark of a capital **L** behind the two words of Latin (**Rosa canina L.**) identifying a plant signifies that it was **L**innaeus who first assigned it the name.

Linnaeus's sexual system for plant taxonomy first divides plants into 24 classes according to the number and arrangement of their stamens and then into orders according to the number of pistils. The orders are then divided into genera and the genera into species. A species, therefore, has a double name in Latin; the first name denotes the genus, the second name the species. The system is known as binary nomenclature. Each genus may have several species, but each species is always unique. The Latin name of the common cowslip is Primula veris and it is one of the species belonging to the genus Primula. Even though Linnaeus's sexual system does not entirely correspond to what we know today about the phylogeny of plants, binary nomenclature is still used. Many of the species names given by Linnaeus are still valid.



Many anniversary books have been produced.

Place of honour is taken by Linnaeus' *signature flower*, *Linnaea borealis* **L.** commonly known as twinflower. Linnaea borealis was given its species name to honour Linnaeus. He called the flower 'my herb' when he saw it during his journey through Lapland, where it was especially common in ancient forests. In his *Flora Suecica Linnaeus* he states that its scent is reminiscent of candy, especially at night, when the scent is so strong that it is recognisable from a considerable distance. Today Linnaea borealis is the provincial flower of the county of Småland where he was born.

Students on *the* UMC's two-week pharmacovigilance course were all presented with a copy of one the many anniversary books, entitled *Linnaeus – Genius of Uppsala*, by Helena Harnesk (Hallgren & Fallgren). *the* Uppsala Monitoring Centre is committed to follow the footsteps of Carl Linnaeus plant classification when recording herbal preparations in the WHO Drug Dictionary, as the binomial system is the only way to communicate the identity of plants between countries globally. Similarly, *the* UMC is classifying all herbal preparations occurring on adverse reaction reports received from members of the WHO Programme all over the world according to the Herbal ATC classification system developed at the Centre. Plants are classified into categories according to their individual characteristics which means that *the* UMC is following and building on the legacy and spirit of Carl Linnaeus 300 years on from his birth.

WHO-FIC meeting

Marie Lindquist reports

A meeting of the WHO-FIC network in Odawara, Japan on 23-24 April 2007 gathered ICD Centre Heads from Australia, Germany, Japan, US and the Nordic Countries, and a number of people connected with the WHO-FIC network, including an observer from the new SNOMED organisation, International Health Terminologies Standards Development Organisation (IHT SDO).

WHO Family of International Classifications (WHO-FIC) refers to the WHO classifications, mainly ICD and those derived from ICD, eg the International Classification of Functioning, Disability and Health, ICF. Related classifications are included in the 'Family', such as ATC.

The ICD organisation is structured around national Collaborating Centres, which perform technical work in production, maintenance and development of the classifications, and which develop national modifications of ICD. The work is planned and co-ordinated by its WHO-HQ secretariat headed by Dr Bedirhan Üstün with Dr Robert Jacob as his assistant. The WHO-FIC network comprises the Heads of the Collaborating FIC centres, the secretariat, and people representing the related classifications and normally meets twice a year.

Ralph Edwards and myself attended in 2005, with the hope of *the* UMC becoming part of the FIC network, and to put the case for an eventual integration of the WHO Drug Dictionary and WHO-ART into future versions of ICD. This time it was possible for me to attend as a WHO-FIC network member.

The meeting was principally to develop a business plan, to be edited and issued as the 2007 version. The meeting looked at funding (or the lack of) and possible collaboration with the new SNOMED organisation. This is needed to achieve the ambitious goals set out for the development of the classifications, including a new ICD-11 (to replace the 20 year-old ICD-10).

The focus of WHO-FIC is currently on:

- Exploring alternative business models for the existing work themes (Information Paradox, ICD Revision, ICD-XM and casemix groupings, ICF, Classifying Interventions, Linkages with Health Terminologies), and two additional themes (Primary Care use of WHO-FIC and Inclusion of Traditional Medicine into WHO-FIC).
- Identification and organization of resources
- Feasibility and Relevance to Stakeholders.

It was agreed that WHO-FIC should continue to pursue and active collaboration with IHT SDO, and that a SNOMED-ICD map would be the most tangible, and likely first practical result. A business development group was formed to spearhead the business development process.

A UMC proposal to include the WHO-Drug Dictionary ingredients list as part of a dynamic ICD was met with a fair amount of interest.

Creation of ICD-11

The revision of ICD has already been agreed. Facilitation of the revision is needed, and the barriers encountered in using ICD-10 are to be properly identified. FIC member countries are the key partners, both current users, and non-users. The end users need to be involved, particularly those involved in statistics production, using formal methods. There is a chance to develop technology during the mapping between ICD – SNOMED which can be reused in the revision process.

Primary care

A working group reported on developments in classifications in primary care. ICD has not been successful in primary care; it needs to adapt to e-health and terminologies, create professional development teams, and provide support for development and maintenance. The primary care market is large, and currently not adequately served. There may be a market, but not necessarily wealthy. It is not about classification, but adding value to the existing clinical work-flow.

Traditional medicine

Dr Kenji Shuto introduced the topic and Dr Watanabe gave an overview of the current activities with regard to the nomenclature and classification of Traditional Medicine. A group under the auspices of WHO Western Pacific Region (WPRO) has been working on this for three years, with four meetings so far. Efforts will be focused on preparation of an alpha version of a classification (ICTC/WPRO) for the October meeting of WHO-FIC. The alpha version will include syndromes and patterns from the terminology (IST) and clinical conditions from the Korean KCKOMe, with maps to IST/ICD10. Dr Watanabe explained that the working group activity has been targeted at harmonisation between the systems used in the key countries (see article on page 10).

In conclusion, Drs Shuto and Watanabe stated that, although they are very familiar with the situation in Japan, there was some uncertainty as to how an international harmonisation between western and eastern medicine should be promoted and achieved. Dr Shuto stated that more work has to be done to explore the possibilities of this theme. The first coding trial has started though, using both ICD-10 and ICTC/WPRO.

The next FIC meeting will be in Trieste from 28 October to 2 November 2007.

Some acronyms

ICD	International Classification of Diseases (WHO)
ICD-XM	Generic term denoting any modified version of ICD, *e.g. ICD 10 CM in the USA*
IHT SDO	International Health Terminologies Standards Development Organisation (the new maintenance organisation for SNOMED)
SDO	Standards Development Organisation, e.g. ISO, CEN, HL7
WHO-FIC	WHO Family of International Classifications

ICH meeting in Brussels

Marie Lindquist

ICH collaboration with ISO

Various work strands of ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) are set to be involved in the more global and wide-ranging activities of the International Organization for Standardization (ISO), following a recent meeting in Brussels.

Recent meetings between the two groups have explored how ISO operates and how the two bodies could collaborate to produce international standards with a wide acceptance. Through mutual recognition agreements, standards approved by ISO are also accepted by CEN (Comité Européen de Normalisation – the European Committee for Standardization) and, since recently, by HL7 (the American health standards organization).

The 'Data Elements and Standards for Drug Dictionaries' (M5) and 'Clinical Safety Data Management - Data Elements for Transmission of Individual Case Safety Reports' (E2B) work items have been accepted as new topics for ISO, which will begin examining them with the first meeting of new ISO task forces in London 7-8 June. This standardisation effort is also supported financially by the European Commission, through a contract with CEN.

MedDRA implementation in Vigibase

At the MedDRA management board (MB) meeting *the* UMC reported on the MedDRA - Vigibase implementation project (for more information on this project, (see the article on page 18). The MedDRA Board was pleased with the progress of the project which will enhance the Vigibase system to be compatible with both WHO-ART and MedDRA.

Collaboration between the EU and WHO-UMC

In connection with the MB meeting, the prospect of further Vigibase enhancements for the EU community users was briefly discussed. Whilst out of scope of the current implementation project, *the* UMC welcomes a dialogue on how to best co-ordinate the work between WHO-UMC and the pharmacovigilance system in the EU. It was agreed, outside the meeting, that representatives from both groups would meet to discuss areas where the two bodies could improve their collaboration.

Pharmacovigilance for clinical researchers in India

The Institute for Clinical Research, India (ICRI) organized a two-day pharmacovigilance training course in Bangalore, India, 12 – 13 April to which Sten Olsson and Ronald Meyboom from *the* UMC were invited. Close to 200 students from Bangalore and the two other ICRI training sites in New Delhi and Mumbai took part in the training. The training course was followed by a conference on 'Clinical Research in India'. This conference also had a session devoted to pharmacovigilance. The commitment of ICRI to pharmacovigilance issues is partly explained by the fact that Dr S K Gupta, formerly head of the Indian National Pharmacovigilance Centre at All Indian Institute for Medical Sciences, is now dean of the institute.

Ronald Meyboom and SK Gupta arriving at the Bangalore course.

In connection with the events in Bangalore Ron Meyboom and Sten Olsson also visited the neighbouring city of Mysore. They gave lectures at the JSS Hospital and were invited by their host Gurumurthy Parthasarathi to take part in a planning meeting for a major research project on drug related morbidity in five hospitals in the state of Karnataka, sponsored by the Indian Institute for Medical Research (see UR 36 p7 for more details).

Sten Olsson and Ron Meyboom with Gurumurthy Parthasarathi (2nd left, front row) and members of his team.

Signals discussed in London

Anne Kiuru

The Drug Safety Research Unit (DSRU) 4th Biennial Conference on Signal Detection and Interpretation in Pharmacovigilance, with the subheading 'Making sense of it all', took place in London with over 90 participants from pharmaceutical companies, national centres and other organizations in Europe and North America.

The objective of the conference was to enable interaction with experts involved in key areas of signal detection and interpretation, while also developing the competence of beginners in the field of pharmacovigilance. The programme covered a wide variety of issues including overview presentations of the different quantitative methods used and recent developments within different organizations and regulations. One session was dedicated to special interest areas and the focus this year was on the signal detection of vaccines and biologicals. The need for anecdotes, spontaneous reporting, clinical trials and epidemiological studies was also discussed, covering several aspects and perspectives of post-marketing surveillance. The two-day conference also contained a few case studies giving the audience examples of the implementation of data mining of different databases of different size organizations representing the perspective of the industry, *the* UMC and the DSRU.

Under the heading "What can we learn from public health 'early warning' systems?" the Global Public Health Intelligence Network (GPHIN) was presented. It is an early warning system for global public health threats worldwide assisting the international public health community by monitoring global media in seven languages. Information on a variety of topics (infectious diseases, contaminated food and water, exposure to chemicals, health related consequences of natural disasters, products, drugs and medical devices safety) is gathered, filtered and reviewed and could therefore be assisting in the timely detection of adverse drug events reported worldwide.

Good Pharmacovigilance Practice and the handling and communicating of signals are still areas in need of further development, so conferences such as this are useful and interesting. I look forward discussing these issues more in the future.

Beginnings in the Eastern Caribbean

Report from Mary Couper

St Lucia was the host country for a recent ARV (anti-retrovirals) Supply Management Training Workshop from 11 to 15 June. This workshop was organized for all the countries of the Organization of Eastern Caribbean States (OECS) - Anguilla, Antigua & Barbuda, British Virgin Islands, Dominica, Grenada, Montserrat, St Kitts & Nevis, St Lucia, and St Vincent and the Grenadines. It was a direct spin-off from the ARV pharmacovigilance workshop we held in Barbados in September 2006.

An entire day on Tuesday 12 June was devoted to introducing the concept of pharmacovigilance, its importance and methods and it is hoped that all the learning objectives were achieved by the end of the day. These were

1) to define pharmacovigilance and its importance
2) to provide a brief description of the methods used
3) to describe how to incorporate pharmacovigilance into the HIV/AIDS program specifically and other Public Health Programmes and
4) to elucidate the key steps in establishing a national pharmacovigilance centre with limited resources.

Dr Julian Pérez Peña, the Head of the National Pharmacovigilance Centre in Cuba, a member of the WHO International Drug Monitoring Programme since 1994 and Naomi Jessurun, National pharmaco-vigilance co-ordinator from Suriname, the latest country to become a member of the Programme at that time assisted me in teaching during that day. By the end of the day the OECS countries had agreed on adapting the reporting form from St Lucia and had appointed focal points for pharmacovigilance in each country.

We can soon expect the OECS countries to be the first cluster of countries to apply for membership of the Programme.

New features in VigiFlow

VigiFlow, the the ICSR (Individual Case Safety Report) management and reporting software from *the* UMC, has reached version 3.2, which contains important improvements from previous versions.

Searching made easier

The most important change for the management of adverse drug reaction reports is the merger of the tools for search and statistics into one comprehensive tool. This will allow users to utilise all functions on the same page. Entered search criteria can be re-used for making different searches and statistical analyses. It is also now possible for a number of statistical output types to be exported to a Microsoft Excel file, so that the results can be subjected to further local analysis.

Security and password

For security, a user who fails to enter a correct password five consecutive times will be locked out of the system for one hour. All users now have the possibility to change their own passwords.

List of reports to be assessed

On both the list of reports to be assessed and the listing of committed reports, report Ids should now be added individually instead of giving a from–to sequence.
National Centres are able to filter ADR reports on the 'list of reports' to be assessed. New functionality is the possibility to filter for reports with a specified sender and to filter reports from more than one Regional Centre (if present) in one search.

Printing reports

A link is now available on the page where confirmation is given that the report has been successfully sent (as committed), which allows the user easy access to a pdf version of that report.

User friendliness

Some small but helpful improvements have also been made to the user friendliness of the software.

Many other changes have also been introduced and all with end user impact are listed in the release notes available from *the* UMC. The User Guide has also been expanded with search and statistics information and the new functionality.

Currently 20 national centres and other organisations are actively using VigiFlow.

MedDRA in the WHO database

Background

The adverse reaction coding terminology in Vigibase, the WHO global ICSR ('individual case safety report') database has traditionally been exclusively WHO-ART. However, following a meeting in September 2005 between WHO and members of the MedDRA Management Board it was agreed that there is a potential loss of information in going from MedDRA (Medical Dictionary for Drug Regulatory Affairs) coded adverse events to WHO-ART. The European Commission (EC) subsequently sent a formal request to the WHO and UMC to implement MedDRA in Vigibase. *the* UMC had already planned for a development which would allow for MedDRA to run in parallel with WHO-ART, but if there was an urgent need for this implementation, additional resources would be required. The MedDRA Management Board considered the provision of resources in order to more rapidly achieve full implementation, and asked for a business plan that would provide the overall approach for the implementation of MedDRA in Vigibase.

Electronic conversion

The adverse event data received by *the* UMC for inclusion in Vigibase is provided by the WHO National Centres, and received in electronic form encoded in WHO-ART or MedDRA. Currently, MedDRA terms are converted to WHO-ART for entry into Vigibase. In the ICH regions, MedDRA has become the standard coding terminology for adverse reactions and for coding indications and disease information for exchange of ICSRs according to the E2B specification.

Compatibility

The goal is for Vigibase processes to be made as compatible with MedDRA as they are currently with WHO-ART. All report data fields currently accepting WHO-ART will be made to allow either WHO-ART or MedDRA terms, and all outputs of these fields will display both WHO-ART and MedDRA. Once that is completed, Vigibase will provide a global repository of MedDRA-coded safety data that can be used as a substantial tool for pharmacovigilance.

Final objectives

The UMC is overhauling Vigibase in other ways which have no direct bearing on the MedDRA implementation project. The scope for *the* UMC development plan for Vigibase is to support fast and reliable reporting of ICSRs into the WHO database, and to maintain and secure the data for short and long term accessibility for analysis and data mining in compliance with regulations and good information management.

The following areas are covered in the overall development plan: import functionality, secure short- and long-term accessibility of ICSR information, and search and analysis methods and tools.

The MedDRA implementation in Vigibase will be outlined during 2007 with a planned delivery during the spring of 2008.

Processing data for entry in Vigibase

All ADR reports sent to *the* UMC today come in predefined file formats. These files are processed and the reports in the files are imported into Vigibase.

The process that was initiated in 2003 has been shown not to be as efficient as we had wished, both in regard to manual work and processing work, so *the* UMC has been trying to improve it. A major reason for changing the process today is that we want to have the report information available for analysis as fast as possible; the old process 'delayed' all correct reports in the same batch as an incorrect report. The new approach would, instead of working with files, focus on the individual reports in a batch and insert the reports immediately in a table in raw data format, for later processing.

The new approach would also make the processing chain work as efficiently as it can. There were problems for example with the number of files, when countries sent multiple files, ie, one report per file, or when countries were sending large files with over 1,000 reports. Another advantage of the new approach is that the reports now can be handled individually and that reprocessing a single report is much easier since it is accessible from the raw data table, compared to earlier, where the report first had to be manually extracted from the original file.

For the national centres an upload interface will be developed during the summer/autumn of 2007 to enable them to upload their files themselves and enter the start and stop dates of the reporting period, along with comments to *the* UMC. The upload interface will be accessible from a username/password protected web page and will also have functionality for presentations of uploading statistics. *the* UMC will still accept reports delivered by CD/e-mail, and *the* UMC staff will then use the upload interface to process the files.

In summary, the major reason for re-building the process again is that it will allow us to have the report information available for analysis as fast as possible.

A new doctor at *the* UMC

Niklas Norén of *the* UMC's Research department has been awarded the degree of Doctor of Philosophy in Mathematical Statistics at Stockholm University. He publicly defended his thesis 'Statistical methods for knowledge discovery in adverse drug reaction surveillance' in an academic dissertation on May 7, 2007. The appointed faculty opponent was Professor Heikki Mannila of Helsinki Technical University.

Niklas's PhD defence.

Niklas received his MSc degree in Engineering Physics from Chalmers University of Technology in 2002, after having written a Master's thesis for *the* UMC on the use of Monte Carlo methods in Bayesian data mining. Over the past five years he has continued to work for *the* UMC on new and improved methods for knowledge discovery in adverse drug reaction surveillance. His doctoral studies were carried out from 2004 to 2007 with Professor Rolf Sundberg at Stockholm University as main advisor and Professor Ralph Edwards as co-advisor from *the* UMC.

From left to right: Rolf Sundberg, Niklas Norén, Heikki Mannila, Ralph Edwards.

Niklas comments "It has been a privilege and an honour to work with two such prominent researchers. They are each excellent sources of inspiration in their respective fields. I also must thank my manager, Andrew Bate, for day-to-day support and advice, and for close collaboration on most of the research included in the thesis".

Niklas's thesis is based on five original scientific contributions that cover different aspects of the knowledge discovery process for adverse drug reaction surveillance. They include a new method for duplicate detection in collections of individual case safety reports, which is now in routine use on the WHO database, improvements to the IC analysis approach to screening the WHO database for excessive ADR reporting rates, and a new measure of disproportionality to highlight suspected drug-drug interaction.

"In my view, the most important contribution is the research and implementation of our new duplicate detection method. The hit-miss model is a very sophisticated approach to record matching, yet its basis for highlighting report pairs as suspected duplicates is very transparent. As such, I think it illustrates knowledge discovery research at its best".

New Master's Thesis

The newest member of *the* UMC team, 25-year-old Ola Caster, successfully defended his Master's thesis in mathematical statistics 'Mining the WHO Drug Safety Database Using Lasso Logistic Regression' on the 7th of June. Ola was supervised at *the* UMC by Andrew Bate and Niklas Norén, and Silvelyn Zwanzig from the Mathematics Department at the University of Uppsala was the official examiner.

Ola Caster

The aim of the thesis was to investigate the usefulness of a particular regression approach to mining the large WHO drug safety database held at *the* UMC. The main difference between the new method and the IC method currently used is that the former is able to simultaneously consider all drugs reported with a certain adverse drug reaction, whereas the latter considers one drug at a time. The main conclusion was that this new method has potential for future practical use despite its complex structure.

Ola, who also holds a Master's degree in pharmacy, has now joined *the* UMC research team where he will stay at least until December 2007.

Utrecht and Uppsala formalize collaboration

Ronald Meyboom reports

Containing real-life observations concerning patients using medicines and experiencing possible adverse drug reactions or interactions, the vast and world-wide collection of data in Vigibase (the WHO database of adverse drug reactions) is a rich resource for scientific study and a tremendous challenge for scientists. Recent research, by Jeroen Derijks, Marieke de Bruin and other scientists of the Division of Pharmacoepidemiology of the University of Utrecht along with *the* UMC, has yielded original and valuable knowledge, ranging from a paper on HERG channels inhibition and torsade de pointes, to work on the use of antidepressants in diabetic patients and their effects on blood glucose.

While in Uppsala last May for teaching at *the* UMC's Pharmacovigilance Training Course, Professor Bert Leufkens, director of the centre in Utrecht, and *the* UMC's Professor Ralph Edwards signed an agreement leading to more intensive future collaboration of both institutes. Utrecht has pharmacovigilance as a priority in its mission and as an under- and post-graduate teaching institute it has a continuous flow of junior and senior scientists with an eager interest in pharmacoepidemiology and drug safety, constituting a large reservoir of high-quality research capacity. The agreement aims at enhancing the use of Vigibase as a data resource in academic pharmacoepidemiology and at developing novel ways of using the WHO database in the scientific exploration of drug-related health issues.

Ralph Edwards and Bert Leufkens sign the agreement.

Although the institute in Utrecht is primarily responsible for training and research, it has close connections with the Medicines Evaluation Board in the Netherlands as well as with the European Medicines Evaluation Agency. Already a member of the EMEA Pharmacovigilance Working Party for several years, Professor Leufkens has recently been appointed Chairman of the Medicines Evaluation Board. Obviously this bridge between academic and regulatory pharmacovigilance will add to the value of the collaboration between Uppsala and Utrecht.

Visitors at *the* UMC

Namibia

On June 7, Mr Jude Nwokike, working for Rational Pharmaceutical Management at Management Sciences for Health (MSH), Washington DC, USA, visited *the* UMC. Mr Nwokike is particularly responsible for MSH support to Namibia and is involved in setting up a drug information and pharmacovigilance centre in that country. To this end MSH supported the participation of Mr Johannes Gaeseb, Drug Registrar of Namibia, in the recent UMC pharmacovigilance training course.

On his way from the USA to Namibia Mr Nwokike passed by *the* UMC to learn more about the services offered by *the* UMC and the WHO International Programme on Medicine Safety. In particular he wanted to know about the functionalities of the VigiFlow system for national management of ADR case reports. On his departure he promised to do his best to facilitate Namibia's attachment as a member of the WHO Programme.

Cecilia Biriell (right) demonstrating aspects of UMC work to Jude Nwokike.

Lithuania

Mindaugas Buta (Head), Evaldas Bogusis (Chief Specialist), Donatas Ragaisis and Ricardas Peldzius from the State Medicines Control Agency of Lithuania came to *the* UMC during a visit to Uppsala for a meeting at the Swedish Medical Products Agency. There was a chance to 'put faces to names' and to discuss areas of mutual interest. They also had a demonstration of VigiFlow.

Lovisa Sällstedt of the UMC (centre) with the Lithuanian delegation.

UMC Publications round-up

The following involving UMC staff have been published in 2007:

Doraiswamy PM, Schott G, Star K, Edwards IR, Mueller-Oerlinghausen B. Atypical antipsychotics and pituitary neoplasms in the WHO database. *Psychopharmacol Bull*, 2007, 40(1):74-6.

Doraiswamy PM, Schott G, Star K, Edwards IR, Mueller-Oerlinghausen B. Erratum: Atypical Antipsychotics and Pituitary Neoplasms in the WHO Database. *Psychopharmacol Bull*, 2007, 40(2):5.

Edwards IR, Biriell C. WHO Programme - Global Monitoring. In: *Pharmacovigilance*, Mann PRD, Andrews EB, eds, John Wiley & Sons, Ltd., 2007: 151-166.

Edwards IR, Star K, Kiuru A. Statins, Neuromuscular Degenerative Disease and an Amyotropic Lateral Sclerosis-Like Syndrome. *Drug Safety*, 2007, 30(6): 515-525.

Hugman B. Tort, error and talk: what can we learn from the litigation crisis? *International Journal of Risk & Safety in Medicine*, 2007, 19: 75-86.

Kelly WN et al. Guidelines for submitting adverse event reports for publication. *Drug Safety*, 2007, 30: 367-73.**

Lindquist M. Use of triage strategies in the WHO signal-detection process. *Drug Safety*, 2007, 30(7): 1.

Norén G N, Orre R, Bate A, Edwards IR. Duplicate detection in adverse drug reaction surveillance. *Data Mining and Knowledge Discovery*, 2007, 14: 305-328.

Olsson S. The need for a generic form for spontaneous reporting of drug related problems. *WHO Pharmaceuticals Newsletter*, 2007, 1: 7-9.

Olsson S. Interview: Ordförande för dem som vill göra skillnad [Chairman for those who want to make a difference]. *Läkemedelsvärlden*, 2007, 3: 30-32.

The Erice manifesto: for global reform of the safety of medicines in patient care. *Drug Safety*, 2007, 30: 187-90.

NB: **this reference has 18 authors including Ralph Edwards

Theses

Niklas Norén. Statistical methods for knowledge discovery in adverse drug reaction surveillance. (Doctoral thesis in Mathematical Statistics at Stockholm University, Sweden 2007).

Ola Caster. Mining the WHO drug safety database using Lasso Logistic Regression. (UUDM Project Report 2007:16. Graduation thesis for Master of Science (Mathematical Statistics) degree at Uppsala University, Sweden).

New staff

Thomas Vidinghoff – Systems Developer

Thomas grew up in the Swedish coastal town of Gävle where his family moved to when he was one month old.

"I have a Masters degree in Computer Science and have worked as a systems and web developer at Telia for three years, and as an IT consultant at WM-data for eight years. My current work is to develop an interface and a web service for uploading reports for a new and improved report import process of the Vigibase Import system."

One of his biggest achievements is to have completed the Stockholm Marathon in four consecutive years. "My goal is to run Stockholm Marathon at least five times so I can receive a five year diploma...!"

At home he has two natural-born tailless cats: a female, Leeloo, and a male, Yabba. They are siblings and their names come from science fiction movies: The Fifth Element (Leeloo), and Star Wars (Yabba, misspelled... actually should be Jabba).

Jeanette Johansson – Signal Detection

Jeanette is a true Uppsala person, having lived in the city all her life.

She has her degree in BSc Pharm from Uppsala University. "Anna Mattson and I were classmates and we decided that it would be nice to work at the same place in the future! I worked at the Apoteket AB (Swedish state retail pharmacies) for a while before coming to *the* UMC. I started off working with the Drug Dictionary, coding drugs etc. Since February I have been a member of the signal detection team, and I really enjoying this aspect of our work!"

Outside of work Jeanette likes to go fishing and to spend time in her greenhouse. The family also have a small breed of rabbit named after the great Portuguese football player Figo. "Two of my boys are regularly playing football and floor ball so there are lots of matches and training practice to attend."

the UMC was unknown to her when she first came to work, "one thing that surprised me was that there are so few people working and so much work done! I like the positive atmosphere at *the* UMC and all the international contacts."

We have said goodbye to Åsa Lindberg, who left UMC in June to work at the Swedish University of Agricultural Sciences near Uppsala.

The WHO Drug Dictionary Training

The WHO Drug Dictionaries have developed over the years and become a *de facto* standard for coding of medicinal products. Many organisations are under pressure to become more efficient and the processes in which the WHO Drug Dictionaries are used are often critical and require prompt management.

New – classroom training

To facilitate an optimal use of the dictionaries *the* Uppsala Monitoring Centre has signed an agreement with PSI International Inc who will provide WHO Drug Dictionary classroom training in addition to the existing web training. The teacher led classroom training will to begin with be introduced in North America.

Web training

The web-based course, 'Introduction to the WHO Drug Dictionaries' has now been running for one year. It introduces participants to basic coding concepts as well as how coding will effect data retrieval. On completion of the course, each participant should have an understanding of the content and structure of the dictionaries, and after passing a 'final exam', receives a certificate. The course takes around 8 hours to complete, although users learn at different speeds, and explore resources and examples at different lengths. The course is accessible for three months after a user name and password are provided.

Learning objectives

Upon completion, the student should have a basic understanding of the codes used in the dictionaries, their structure and the different formats. The student should also get basic knowledge of the Anatomical Therapeutic Chemical (ATC) Classification.
The course also enables students to:

- understand what types of medicinal products are included in the dictionaries and hence which verbatims are likely/unlikely to find a match in the dictionaries
- understand the need for coding herbal remedies and benefits of WHO Herbal Dictionary.

Testing

Every chapter ends with a 'Test your knowledge' section. The exercises can be repeated and are followed by comments to clarify the examples.

Ordering the course

The web shop has more information (see www.umc-products.com/training). If you have questions, please contact training@umc-products.com

User Group

The User Group Portal on www.umc-products.com/training assists both new customers and experienced users. It contains a library of articles and documents related to the User Group, advertises forthcoming User Group Meetings and has a discussion forum (you will need a password to register).

Meet the team

Staff from UMC Products and Services are planning to be at the following conferences in the coming months, please feel free to visit our booth:

- August 19-22, 2007
  ISPE Annual Meeting, Quebec City, Canada
- September 16-19, 2007
  2007 SCDM Fall Conference, Hyatt Regency Chicago on the Riverwalk, Chicago, Illinois
- October 14-19, 2007
  17th Annual CDM EuroMeeting, Auditorium Madrid Hotel, Madrid, Spain

Daniel von Sydow, Annika Wallström and Mats Persson on the UMC stand at the DIA meeting in June.

If you have any questions or if you want to meet us in connection with the above meetings, please contact Mr Mats Persson, Head of Sales & Marketing: mats.persson@umc-products.com

WHO Dictionaries, June, 1-2007 release

The WHO Drug Dictionaries are released on a quarterly basis. The June 1 release is the second this year – the first was released on March 1. The June 1 release contains 15,181 new entries since the March 1 release – and 69,315 new entries since June 1 2006.

Need help?

If you have any queries about WHO-DD, or need further information about your current subscription or how to upgrade it, do contact us.

You can e-mail:
drugdictionary@umc-products.com
for comments about the WHO-DD, WHO-DD Enhanced, corrections and additions, and
katarina.hansson@umc-products.com
for queries about your subscription.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
19-22 August 2007	23rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Quebec City, Canada	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com http://www.pharmacoepi.org/
31 August 2007	Workshop: Strategies in Medication Safety – Pharmacovigilance / Preventing Medication Errors *(part of the 67th International Congress of FIP)*	Beijing, China	International Pharmaceutical Federation (FIP) www.fip.org/CONGRESS/beijing2007/index.php?id=600
5-8 September 2007	Linnaeus and Medicinal Products: An international conference on drugs of natural origin	Uppsala, Sweden	Details, Tel: 08-723 50 00. Fax: 08-20 55 11. E-mail: info@lakemedelsakademin.se
12-13 September 2007	Back to Basics in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
16-19 September 2007	The Society for Clinical Data Management (SCDM)	Chicago, Illinois, USA	Society for Clinical Data Management (SCDM) www.scdm.org/
17-18 September 2007	Adverse Event Reporting and Pharmacovigilance	London, UK	IIR Tel: +44 (0)20 7017 7481 Email: registration@iir-conferences.com
18 September 2007	The Role of the Qualified Person in Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 Website: www.management-forum.co.uk
19-20 September 2007	Advanced-level Adverse Event Reporting & Pharmacovigilance	London, UK	IIR PTI Tel: +44 (0)20 7017 7481 Email: registration@iir-conferences.com
26 September 2007	Drug Safety Surveillance	Washington DC, USA	DIA www.diahome.org
26-27 September 2007	Critical Appraisal of Medical and Scientific Papers: How to read between the lines	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
3-5 October 2007	Advanced Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 Website: www.management-forum.co.uk
10-11 October 2007	Risk Benefit Assessment in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
16-26 October 2007	Counterfeit medicine control and law enforcement	Canberra, Australia	TGA http://www.tga.gov.au/docs/html/inttrain.htm
21-24 October 2007	7th Annual Meeting of ISoP	Bournemouth, UK	Hampton Medical Conferences Ltd Tel: +44 (0)20 8979 8300 Fax: +44 (0)20 8979 6700 E-mail: isop2007@hamptonmedical.com Website: www.isop2007.org
14-15 November 2007	Case Narrative Writing for Reporting Adverse Events	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
26-29 April 2008	The International Society for Pharmacoepidemiology (ISPE) Announces its 2008 Mid-Year Meeting	Boston, USA	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com http://www.pharmacoepi.org/
6-8 October 2008	8th Annual Meeting of ISoP	Buenos Aires, Argentina	ISoP Tel/fax: +44 (0)20 3256 0027 E-mail: administration@isoponline.org www.isoponline.org

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