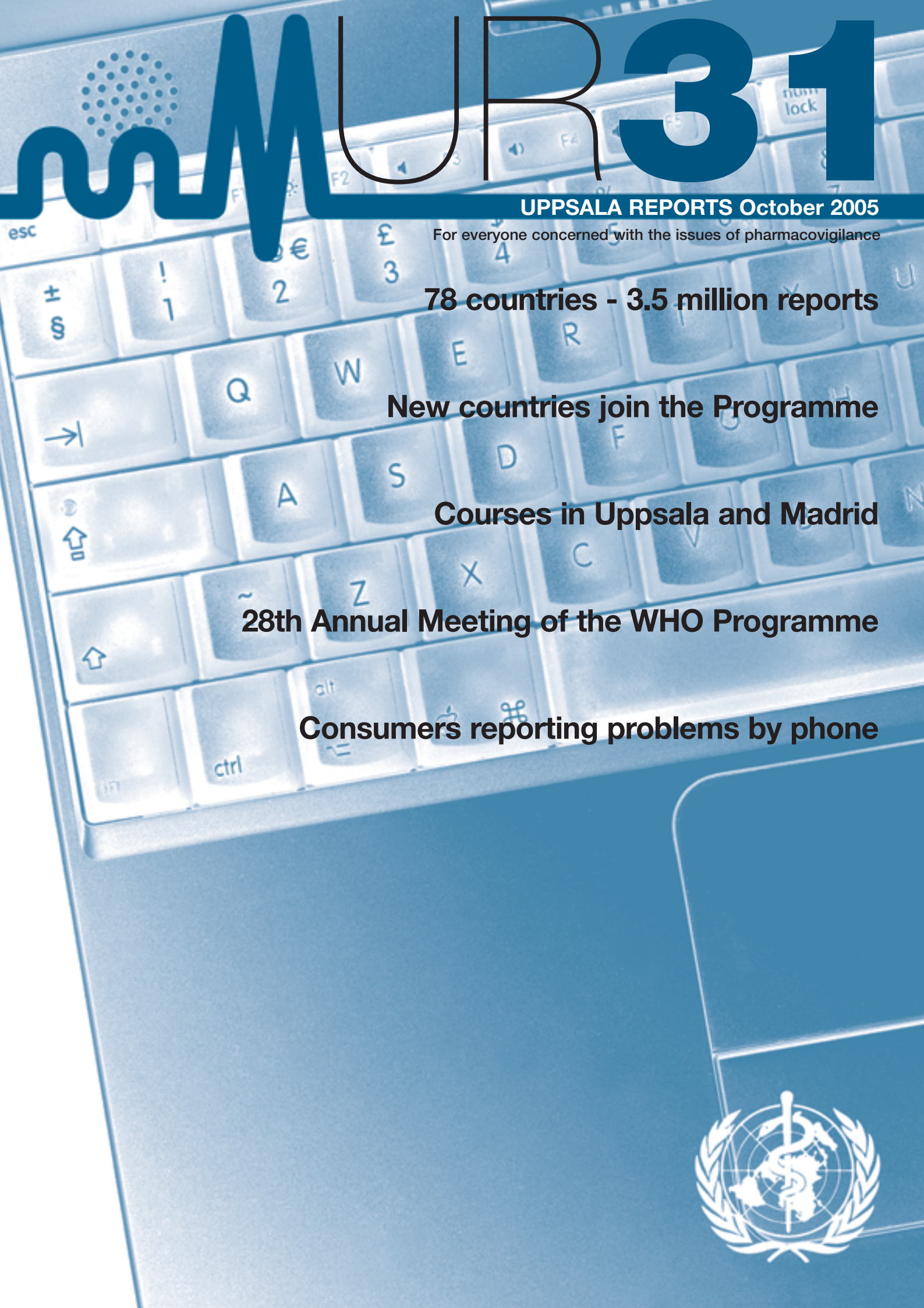


WHO UR 31

UPPSALA REPORTS October 2005

For everyone concerned with the issues of pharmacovigilance

78 countries - 3.5 million reports

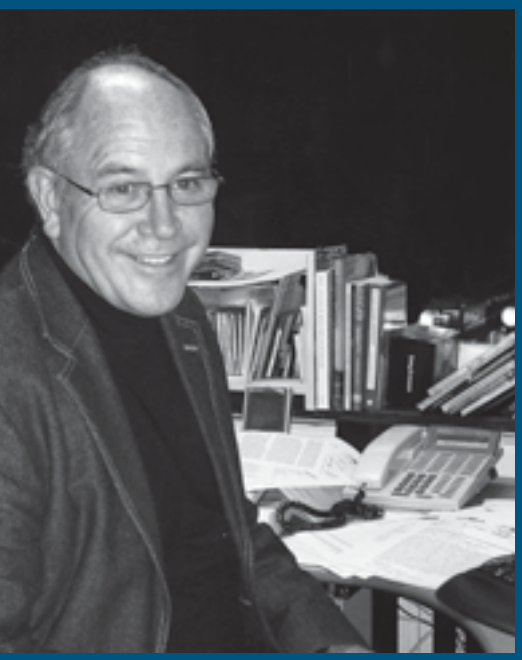
New countries join the Programme

Courses in Uppsala and Madrid

28th Annual Meeting of the WHO Programme

Consumers reporting problems by phone

DIRECTOR'S MESSAGE



Ralph Edwards
Director
the Uppsala Monitoring Centre

I have just returned from the 28th Annual Meeting of the countries involved in the WHO Programme for International Drug Monitoring, held in Geneva. A keynote address was given by Sir Liam Donaldson, who is the Chairperson of the WHO Global Alliance on Patient Safety. He presented several powerful stories – including video clips – to illustrate the harm caused by medication error. Delegates debated what Programme members might do to expand their work from merely looking for new adverse drug reactions, to getting information on how therapeutic accidents occur and how they may be prevented. I have previously mentioned the start of the Alliance in UR27, October 2004.

There was a critical, though positive, reception to broadening pharmacovigilance in this direction, but many thought that patient safety was already a main focus of what we do. Confidentiality of reporters, the problems of blame being apportioned, ensuing litigation, the possible negative effects on reporting systems were just a few of the problems foreseen. And yet there was a keenness to tackle the challenge of preventable ADRs continuing to be a major source of mortality, morbidity and cost in health care.

Our Annual Meetings always have several sessions where countries bring new areas of concern to share and discuss with colleagues, called 'Drugs of Current Interest'. I reckoned that 11 out of 25 of these topics had a strong patient safety element, including examples such as three cases of virilization of young children via secondary accidental contact with a topical testosterone preparation used by the fathers, and another of recurrent penile ulceration in a man taking an new anti-inflammatory. This latter case is probably a severe example of a fixed drug eruption, which often affects the genitals alone, and was not recognised as causally linked to the drug – in spite of four re-exposures! There were three presentations where deaths were caused by medication error, and one related to possible syringe contamination and occurring in some medical equipment. These examples and others, I believe, strongly emphasise the patient safety focus in what we do.

The outcome of discussion at the meeting was to institute a pilot project to run for two years. The project will involve about ten national centres and be coordinated by the UMC. The aims will be to examine the possibilities and consequences of broadening the scope of pharmacovigilance to get reports of medical error, as well as to increase the depth of investigation into one or more of the common areas where medication error is a stronger possibility (drug interactions are but one area to consider). It is planned to produce a protocol for the study by the end of the year, and hoped that we will have not only information about the feasibility of this type of work, but also examples where situations encountered led to actions that may reduce future risks globally.

It was also very pleasing to hear in Geneva much support for the UMC's IT work. Vigibase Online is used by more and more centres as a way of handling and exchanging patient report information in the ICH E2B format. Eleven centres are using it, both large and small, and much satisfaction was expressed about the ongoing sound development of this tool. There is now a strong interest by industry users for this web-based system, which also allows seamless, secure primary reporting by health care professionals to a subsidiary (or regional centre), and on to any selected recipients. Another success was the presentation of our new duplicate detection tool. This won first prize at the major international meeting on knowledge finding[1] , and it has been tested in a 'live' drug safety data set.

Finally, it is wonderful to see the growing number of countries joining the Programme and actively participating in the meetings in a most friendly and mutually supportive way. I congratulate all those who were involved in the meeting, and I am honoured to play a continuing part of their endeavours.

1. Norén GN, Orre R, Bate A. A Hit-Miss Model for Duplicate Detection in the WHO Drug Safety Database. In: Proceedings of the Eleventh ACM SIGKDD International Conference on Knowledge Discovery and Data Mining; 2005; Chicago, IL; 2005.

7

WHO Programme meets in Geneva

A record number of delegates from countries participating in the WHO Programme for International Drug Monitoring met in Geneva in September for intense debate and discussions

10–11

UMC team around the world

Reports from some of the major conferences where members of the UMC team have participated

12–13

Consumer reporting by phone

Report from an interesting and successful project in Australia with data on ADRs direct from patients

21–22

Drug Dictionary advances

Reports on the new WHO Herbal Drug Dictionary and the massive increase in entries for the WHO Drug Dictionary Enhanced

3.5 million reports

In September 2005 the WHO Programme for International Drug Monitoring reached 3.5 million adverse drug reaction (ADR) reports in the international database. All the countries that belong to the WHO Programme commit to work together to monitor the safety of medical drugs and to send reports of adverse reactions involving medical products to the WHO Collaborating Centre in Uppsala. The first ADR entered the WHO database in 1968; every report is vital to the work of the Programme, wherever it comes from.

and more countries join the Programme

Since our last Uppsala Reports, three countries have joined the Programme as full members and three others have become Associate Members - details on pages 4 and 5.

CONTENTS

the UPPSALA MONITORING CENTRE

Communications information

Postal address:
the Uppsala Monitoring Centre
Stora Torget 3
S-753 20 Uppsala
Sweden

Telephone: +46 18 65 60 60

Fax: +46 18 65 60 80

E-mail:
General enquiries: info@who-umc.org
Personal e-mail messages may be sent to any member of the team by putting their name (e.g ralph.edwards) in place of info

Internet: www.who-umc.org

Sales & marketing enquiries: info@umc-products.com

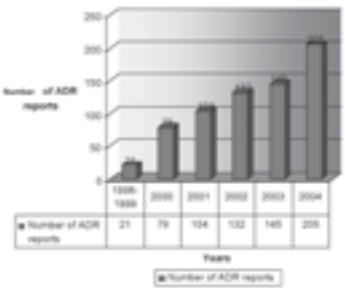
ISSN 1651-9779

Introducing Lithuania

76th Member of WHO Programme for International Drug Monitoring

Lithuanian pharmacovigilance staff: (seated) Margarita Maskeliunaite, Head of the Post-Authorisation Evaluation Unit, (standing from left) senior specialists: Vilma Prialgauskiene, Mindaugas Buta

Baltic showing Lithuania



Number of ADR reports in Lithuania

An independent state between the world wars, the Republic of Lithuania became the first Soviet republic to declare independence from the Soviet Union in March 1990. Located on the Baltic Sea with a population of 3.5 million, it was one of ten countries which joined the European Union in May 2004.

History of drug monitoring

The State Medicines Control Agency of Lithuania (SMCA) was established in 1995. The main objective of the SMCA is to control pharmaceutical activity in order to ensure the quality, efficacy and safety of medicines available in Lithuania, to pursue the National Medicines Policy Program as well.

Although ADR reporting was defined in the Drug Law of 1996, pharmacovigilance activities mainly began in 1999 with participation and training in Pan-European Regulatory Forum (PERF) meetings. Initially, a legal basis was created which regulates the national pharmacovigilance network: ADR reporting became obligatory for health care professionals (2001) and marketing authorisation holders (2002). A 'yellow card' form based on CIOMS I was approved for reporting of serious and/or unexpected ADRs, with a reporting time of 15 days. Generally, the pharmacovigilance system is centralised, with all ADR reports being sent to the SMCA. Since that time reporting has increased each year: in 2001 we received 104 ADR reports, in 2004 205 reports, and this year until July, 259 ADR reports.

Plans for development

SMCA continues promoting spontaneous reporting: it has created a free-post service for spontaneous ADRs and informed 1,000 nominated health care professionals by a letter, allotting a free fax number for reporting. The ADR report form is easily available from the SMCA's website, and is provided via individual medical journals from time to time.

There are educational activities – SMCA publishes a pharmacovigilance bulletin, and a handbook of methodological recommendations for health care professionals has been prepared. 10,000 copies of this handbook will be published, and all doctors in Lithuania will receive it free of charge. We want to acquaint every doctor with basics of pharmacovigilance and get them involved more actively.

Evaluation Unit established

During recent years, the need for a separate unit responsible for pharmacovigilance and post-authorisation issues of medicinal products within the SMCA emerged. In 2004 the Post-Authorisation Evaluation Unit within Marketing Authorisation Division was established.

The staff of seven now consists of: three medical doctors, mainly responsible for collection, collation and evaluation of spontaneous ADR reports, risk assessment, regulatory action and risk communication; three pharmacists and one administrative assistant mainly involved in variations and other changes of the dossier of authorised medicinal products.

Our future work will concentrate on international collaboration - in 2005 SMCA started testing electronic reporting with European Medicines Agency (EMEA) according to ICH E2B standards. In July the SMCA fulfilled WHO requirements and became a member of WHO Programme for International Drug Monitoring. An exchange of drug safety information will help us take regulatory decisions in time and improve rational and safe use of medicines.

Margarita Maskeliunaite
Head of the Post-Authorisation Evaluation Unit
State Medicines Control Agency
Traku Street 14
Vilnius 01132 LITHUANIA
Tel. +370 5 2639264, +370 5 2639053
Fax: +370 5 2639265 www.vvkt.lt

Mozambique

The national pharmacovigilance centre in Mozambique, headed by Dr Esperança Sevene, has been active in pharmacovigilance training in several provinces of the country and interacting with the national programmes against malaria and HIV/AIDS. Reports have now started to reach the UMC through Vigibase Online.

Contact: Drug Information Center (CIMed), Av. Salvador Allende n. 702, Maputo, Mozambique, E-mail: esevene@health.uem.mz

Brunei Darussalam

Brunei–Darussalam is a small country of 350,000 on the island of Borneo. It has had a drug information, poison information and pharmacovigilance centre since 1998 and the first ADR reports have now been submitted.

Head of the centre is Ms Asma A'tiyah Haji Abdul Hamid, Drug & Poison Information Section, Department of Pharmaceutical Services, Raja Isteri Pengiran Anak Saleha Hospital, Brunei Darussalam, E- mail: aatiyah@brunet.bn

Turkey scaling up activities

In July 2005 Turkey introduced new regulations for pharmacovigilance activities. The new rules are designed to be in harmony with the pharmacovigilance system that applies within the European Union, as Turkey was this year accepted as an official candidate for accession to the EU.

According to the new regulations pharmaceutical companies are required to submit reports of suspected serious adverse drug reactions to the national pharmacovigilance centre (TÜFAM), within 15 days. They also have to submit Periodic Safety Update Reports (PSURs) to the Turkish Ministry of Health with the same frequency as within the EU. The upgraded pharmacovigilance system also includes a rule that all hospitals of 50 beds or more (university hospitals, other training and research hospitals and private hospitals of 'A-1' group) are required to have a pharmacovigilance officer responsible for submitting adverse reaction reports to TÜFAM. A 12-member Drug Safety Advisory Committee has been established, meeting about once every two weeks. TÜFAM has decided to employ Vigibase Online, the internet based system for case report management developed by *the* UMC, for processing of national data and for reporting to the WHO.

Turkey joined the WHO International Drug Monitoring Programme in 1987 when the Turkish national centre for adverse drug reaction monitoring, TADMER, was established. However the reporting rate was never very high. Changing the name of the centre to TÜFAM, the Turkish Pharmacovigilance Centre, is a way of emphasizing that the scope of the new centre is wider than that of TADMER. Head of the centre is Demet Aydinkarahaliloğlu (pictured). She is assisted by two young pharmacists, Arzu Karslioğlu and Emel Aykaç. They have plans of expanding their activities in promoting adverse drug reaction reporting from all over Turkey.

A few days after the new pharmacovigilance regulation was put into force, on July 8, the Ministry of Health organized a training seminar in Istanbul to provide advice and guidance to qualified persons from the pharmaceutical industry and to pharmacovigilance officers from Turkish hospitals. The training focused on definitions, regulations and processes for adverse reaction reporting. The importance of Turkish participation in international networks was also emphasized. TÜFAM had invited Jan Petracek from the Czech Republic and Sten Olsson from *the* UMC to provide international perspectives. Dr Petracek outlined both the EudraVigilance system the EU and of the operation of pharmacovigilance in the Czech Republic. Sten Olsson summarized the functions of the WHO pharmacovigilance network and the system used at *the* UMC for signal identification and analysis. The training seminar was chaired by Dr Seyfullah Dagistanli, Head of Quality Control Department of the General Directorate of Pharmaceuticals and Pharmacy, Ministry of Health, Turkey.

Three new Associates

Mongolia

In issue 27 of Uppsala Reports, October 2004, we had a short report about adverse reaction research carried out in Mongolia. The Mongolian Ministry of Health has formally applied for them to be admitted as a member of the WHO Programme and so Mongolia now has Associate Member status while we await their first adverse reaction reports.

Contact: Dr Nanjaa Tsogzolmaa, Department of pharmacy and medical equipment, Government building-8, Ministry of Health, Olimpic Street-2, ULAANBAATAR 210648, Mongolia, Tel: +976-11-321 093, Fax: +976-11320 633, Email: iltbih@yahoo.com

Uzbekistan

At the end of May, the Ministry of Health in Uzbekistan submitted a formal application to join the WHO International Drug Monitoring Programme. This means that Uzbekistan will be regarded as an Associate Member Country of the Programme. This is a direct effect of Sten Olsson's visit to Moldova in April (reported in UR30).

The Pharmacological Committee (chaired by Professor Bakhtiyor Shoislamov) are looking forward to co-operation with the Programme, which will give great support in their work. Uzbekistan are hoping to become full members of WHO Programme within a year.

Contacts are: Prof. AA Tulaganov, Chief of the Head Department of Drug and Medical Equipment Quality Control (HDDMEQC), Usmankhodjaev str., K.Umarov passage, 16. 700002, Tashkent, tel: 1444818.

Prof. Bakhtiyor Shoabdurakhmanovich Shoislomov, Chairman of Pharmacological Committee of HDDMEQC, Curator of Adverse Reaction Monitoring Commission, Usmankhodjaev str., K.Umarov passage, 16. 700002, Tashkent, tel: 1444823, 494668, e-mail: BShaislamov@yandex.ru

The technical representatives are members of the Adverse Reaction Monitoring Commission, Dr Doncheva Elena Fedorovna and Dr Ayzikov Moisey Ilyich, Usmankhodjaev str., K.Umarov passage, 16. 700002, Tashkent, tel: 1444823, 494668,

Sierra Leone

In August Sierra Leone formally applied for membership of the WHO Programme. Sierra Leone has submitted its application as a direct consequence of *the* UMC training course in May 2005. Wiltshire Johnson, who attended, has convinced his Pharmacy Board to set up a Drug Information and Pharmacovigilance unit and to apply for membership in the WHO Programme. The contact details are:

Wiltshire C N Johnson
Drug Information and Pharmacovigilance Unit
Pharmacy Board of Sierra Leone
P.O. Box 322 Freetown Sierra Leone

Tel: +232-22-225983/228497 +232-76-602031
Fax: +232-22-224526
e-mail: infopharm_pbsl@yahoo.com

The set-up in Algeria

Professor A Helali, of the Centre National de Pharmacovigilance et de Matériovigilance in Algiers has sent us some information on current activities in Algeria.

The watching system for the safety of medicines and medical devices in Algeria is the responsibility of the Centre National de Pharmacovigilance et de Matériovigilance (CNPM), created in June 1998.

Bulleting d'Information de Pharmacovigilance et de Matériovigilance

The centre undertakes to:

- monitor adverse reactions due to the use of medicines or vaccines marketed in the country (pharmacovigilance);
- monitor incidents or risks of incidents resulting from the use of the medical device marketed (materiovigilance)
- implement research to establish the causality of adverse reactions or incidents.
- Improve knowledge and skills in therapeutics in order to promote the rational use of medicines, vaccines and medical devices.
- Report fraudulent or misleading advertisements of medicines.

Its main tasks are:

1 To improve the medicines security through a supervision system of undesirable effects,
2 To improve the rational use of medicines and the management of diseases,
3 To improve medical device performance and security:

The Algerian network is composed of:

- A central organization, which permits the concentration and treatment of information from the physicians, and organize investigations to establish the relationship between undesirable effects and suspected medicines.
- Decentralized activities via regional technical collaborators (43 areas around the country), conducting compilation of incidents and undesirable effects.

Collaborating members have been trained during regional seminars which have taken place since the creation of the centre. The teaching of pharmacovigilance is based on solving problems in order to learn how to establish the relationships between adverse effects and the medicine responsible. The problem–based method offers the participant knowledge and skills in pharmacovigilance and in problem-solving approaches.

For ten years, training in rational prescribing has been given to sixth-year students in medicine (before clerkship period into graduate study). Knowledge and skills in rational prescription and dispensing, and promoting the pharmacist-physician collaboration in chronic diseases was given at a summer course for French speaking countries in Africa with the co-operation of the WHO; a national network for promotion of rational use of medicines was created in 2004.

Finally, the centre has published a 'Dictionnaire Commenté des Médicaments' (a 307-page textbook dealing with benefits of each new medicine in the Algerian market), a 'Guide des Intéractions Médicamenteuses' and a quarterly 'Bulletin d'Information de Pharmacovigilance et de Matériovigilance' (see illustration).
The contact is:

Centre National de Pharmacovigilance et de Matériovigilance B.P 247
Centre Hospitalier Universitaire de Bab El Oued 16009 Algiers

E- mail: pharmacomateriovigilancedz@hotmail.com or vigilances_dz@yahoo.fr

Change in Costa Rica

The National Centre for Costa Rica has been transferred from Caja Costarricense del Seguro Social to the Ministry of Public Health. The new official channels of communication are:

Dirección de Vigilancia de la Salud
Ministerio de Salud Oficinas Centrales
PO Box 10123-1000
San José
Costa Rica
Tel: +506 2211662

The co-ordinator is Dr Adolfo Ortiz Barboza assisted by Dra Xiomara Vega.

Costa Rica is hoping for continuing collaboration with the WHO Programme and strengthening of pharmacovigilance activities.

Delegates during a working group in the Executive Board Room at WHO HQ, which was also the main room for plenary sessions. Posters, books and leaflets were on display outside this auditorium, and working groups took place in seminar rooms around the WHO building, including one with spectacular views over Geneva and the lake.

28th Annual Meeting of National Centres

Bruce Hugman reports from Geneva

The Executive Board room at WHO Headquarters was the imposing setting for this year's meeting. 45 countries participating in the Programme were represented by a total of 72 individuals, along with WHO and UMC personnel. Challenging topics were addressed, along with a range of more specific and technical concerns. Dr Vladimir Lepakhin, the Assistant Director General, opened the meeting and showed his support by his presence during many of the sessions. Holding the meeting in Geneva allowed the involvement of almost all the other departments within WHO, and provided an opportunity to strengthen collaborations and widen the scope of pharmacovigilance activities through the Organization.

Among the big issues was the place of patient safety as a priority for international pharmacovigilance. The topic was vividly presented by Sir Liam Donaldson, whose driving concern was the reporting, analysis and understanding of patient injuries of all kinds caused by medical intervention and possible steps to reduce their number. Ralph Edwards' Director's Message on page 2 covers this in more detail.

Working groups addressed a wide range of problems. Among these:

1. the impact and effects of high profile drug withdrawals, especially on countries outside the circle of big players
2. the challenges of developing a patient safety event taxonomy
3. the closer linkage of pharmacovigilance classifications with others such as ICD10 and INN
4. the need for a higher level of collaboration between pharmacovigilance programmes and public health programmes such as HIV/AIDS, malaria, TB and parasitic diseases (see box)
5. the improvement of reporting of adverse events following immunisation (AEFI) to the WHO database (Vigibase) and the refining of terms to facilitate this.

Improvement of the quality of spontaneous reports was discussed along with new methods for identifying duplicates in large databases. (the UMC team had recently won a best application paper at the KDD international conference in Chicago for development of an automated method of achieving this.)

The latest version of the UMC E2B-compatible, web-based tool for ADR reporting, Vigibase Online, was presented and demonstrated and stimulated considerable interest. Already it is in use by eleven countries and this number is set to expand.

'Problems of Current Interest' focussed attention on specific problems which as always sparked much debate. This year's topics included:

Injectable ibuprofen and tissular necrosis
Virilization in children whose father used a testosterone preparation
Eterocoxib and ulceration of the penis
Benzyl alcohol for muscle injection
Puerarin injection and anaemia
Levamisole and encephalitis
Chelidonium-based herbal drugs
Ezetimibe and myopathy
Anaphylaxis and fluoroquinolones
Mirena®
Fluvastatin and hepatotoxicity
Influvac – neuralgic amyotrophy
Local reaction to flucloxacillin
Aripiprazole and suicide
Oral allergen-specific immunotherapy
Vancomycin-induced 'red men syndrome'
Carisoprodol and abuse
Hops and menstrual haemorrhage

These topics represent concerns from national centres, currently without resolution of the questions or establishment of causality.

Presentations from Ghana, the EU and the USA FDA reflected on the lessons learned from rofecoxib. For Ghana, the question of the safety of generic rofecoxibs on the market, following the withdrawal of the patent holder's product (Vioxx) was an issue (see box).

Vivid cases from Sri Lanka highlighted how the reporting of adverse events may make a large contribution to patient safety when information is analysed and followed-up and root causes identified. The meeting heard also, to its astonishment, that in one small post-tsunami study of donated drugs in Sri Lanka, 4.5 million packs were scrutinised, many of which had passed their expiry date (a few by 35 years) and that many were, in any case, irrelevant in the absence of epidemics and other widespread public health needs.

The 2006 meeting was announced to take place in Liège, Belgium, from 9-11 October, followed by the Annual Meeting of the International Society of Pharmacovigilance.

Rofecoxib

Both the presentation from the US FDA and the EU pharmacovigilance working party made the point about the complexity of finding a signal on an adverse event with a high background rate (cardiovascular disease). Whilst spontaneous reporting had been excellent at raising the hypothesis, epidemiology was an essential tool for further analysis. That there were several new drugs in the same COX2 class was a complication; that controls were problematic (being other drugs which may have an effect, positive or negative on cardiovascular disease); and that the widespread use of low dose aspirin complicated the picture were some of the matrix of challenges to rational effectiveness risk decision-making for public health.

Whilst the EU presentation focussed more on the need for clarity in process, the FDA addressed the deficiencies in currently available tools. A proposal for wider use of patients record databases was made.

Ghana focussed on international collaboration. A decision by the USA, EU or other major developed country has huge repercussions on public health practice and public perception and trust in other countries. The proposal was made that true international collaboration would lead to a reduction in international disharmony in regulatory decisions, by sharing and therefore cut the time from signal to effective public health action.

Public health challenges:

In several public health programmes that employ mass drug administration:

- Many new drugs are used to treat HIV/AIDS, Malaria, TB and helminthic infections
- Drugs are used in combinations not assessed in developed countries
- There is incomplete knowledge on the safety issues with these drugs
- There is no planning to include a Pharmacovigilance component in these public health programs

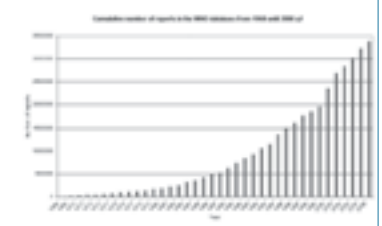
Solutions:

- Building into specifications for public health programmes a requirement for pv assessment
- Concept of Pharmacovigilance planning (ICHE2E) to be taken up and used to develop a system for meeting the needs of specific infectious diseases and drug treatment safety concerns

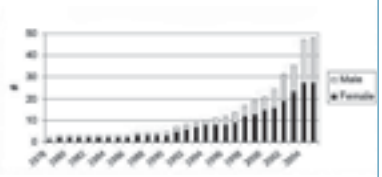
The plan may include active, targeted surveillance programmes.

Driving the vision of *the* UMC

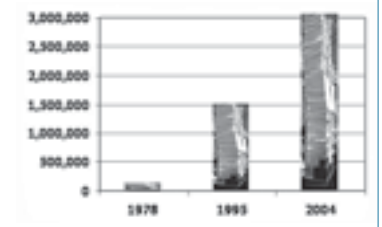
Lars Magnusson, Ralph Edwards and Marie Lindquist



Cumulative number of reports per year in Vigibase June 2005



Cumulative number of UMC employees



From 1978 to 2004 there was a vast increase in the number of reports in 'Vigibase' - the WHO database of adverse drug reactions. The number of member countries of the Programme also increased during this period.

In a changing world, *the* UMC is continuously reviewing its vision and priorities to ensure that its work meets the contemporary and future needs of drug safety professionals and patients. Many major changes and developments have taken place in international pharmacovigilance since the early days in the 60s and 70s, and many have been influenced by the leadership of *the* UMC.

Now, *the* UMC Executive Committee is consulting with its worldwide constituents and the staff at the Centre about future direction and priorities.

Here, we share with you some of the thinking, invite your comments, and also introduce you to the three people responsible for the overall effectiveness of *the* UMC's work.

Putting patients first

Since the WHO Programme began, the gaze of member countries and of *the* UMC has been on drugs used in medical practice, particularly new drugs, in order to find new, unexpected (and usually relatively rare) adverse reactions.

Over the years, and particularly since the number of developing country members has grown, we are constantly reminded that many ADRs are preventable and that the main culprits are often old drug groups. Attention has also been drawn to overdose and misuse of drugs; off-label prescribing; foreseeable drug interactions; reactions in specialist areas such as ENT (ear, nose and throat); OTC drugs; reactions which did not lead to hospital admission, and herbal medicines. Overall, we know that about half the reactions that lead to hospital admission are preventable.

The end goal of 'drug safety' has always been patient safety, but the emphasis has been on what was wrong with the drug. We have traditionally collected much less information about how the drug was prescribed, dispensed and used. While we have talked (and taught) a good deal about the importance of improved methods and materials of communication in improving patient safety, radical and effective change in practice has not really followed.

The establishment of the WHO Global Alliance for Patient Safety , and the likely involvement of *the* UMC in collection of more data about patients (not the least via ICH E2B reports), sets the scene for the broadening of the concerns of pharmacovigilance to include a much greater focus on patient safety issues, on the concerns which doctors and patients have about medicines. This in no way reduces the importance of established standards of spontaneous reporting of suspected ADRs, but rather broadens and enriches the usefulness of data available in the pursuit of safe and rational therapy.

Taking *the* UMC into new territory

The current and developing enterprise is in the hands of *the* UMC's Executive Committee: Ralph Edwards, Marie Lindquist and Lars Magnusson. Here are pen portraits of them to give you some idea of experience and skills behind the policy and activity of *the* UMC (not forgetting the skills and experience of the nearly fifty members of staff without whom nothing could be achieved at all).

Professor Ralph Edwards, Director

Ralph Edwards' particular strength is in his broad range of international clinical and research experience. This was developed from his days as a junior doctor and then consultant in Sheffield, England, through to his work as Professor of Medicine at the University of Zimbabwe. His concern for patient welfare and his clinical acumen have never left him.

In New Zealand he ran the national pharmacovigilance and poison centres which took him deep into both pharmacology and toxicology, and brought familiarity with a range of medical and chemical problems.

Senior posts always bring with them the challenge of leading and managing organisations effectively. Heading up university departments, running a small 'science park' enterprise and national organisations in the past, now steering *the* UMC, Ralph Edwards has accumulated considerable organisational wisdom and skills. Linked with a visionary capacity, his strategic thinking, his experience, persistence and business skills give him powerful credentials for his present post. That he has, from time to time, been enmeshed in controversy and has crossed swords with some pretty impressive people, demonstrates only his level of conviction and determination to find the best solutions for science and for patients.

Beyond work, he is also pursues life with energy and meticulous attention to detail: he is a great reader and thinker; he is a skilled yachtsman and conservation falconer; he paints and can tackle almost any mechanical engineering problem – a breadth of talent and sympathy unusual in any professional.

When he took up post as Director in 1990, *the* UMC employed a total of four people. Now with fifty staff, and almost eighty member countries in the WHO Programme, and entirely dependent on their own efforts for income (there is no external funding of any kind), it's evident that Ralph Edwards has served *the* UMC and the international pharmacovigilance community exceptionally well.

Dr Marie Lindquist: Deputy Director and General Manager, Science and Technology

Marie Lindquist joined the original two members of staff, Sten Olsson and Cecilia Biriell, one year after the WHO Collaborating Centre for International Drug Monitoring (now *the* UMC) moved to Sweden in 1978.

She has had practical, hands-on experience of every aspect of *the* UMC's work, including data-entry and management, classifications and terminologies, signal detection methodology and research in many areas of drug safety. She has also been actively involved in most of *the* UMC IT development over the years, ranging from setting up drug safety related databases to administrative support systems. In the 1980s she spent a year in the Swedish Medical Products Agency's pharmacovigilance section under Bengt-Erik Wiholm's leadership, gaining first-hand knowledge of the operation of a national regulatory agency.

In many ways she is the perfect complement to the Director, particularly bringing depth to his breadth. She is a meticulous planner and organizer and relishes the challenge of translating ideas and policies into practical action. She is responsible for the day-to-day operation of the scientific division and for the scientific staff, with an obsession for quality and a detective's approach (Sherlock Holmes is one of her heroes) to seeing, observing and interpreting evidence. In 2003 she completed her PhD 'cum laude' - with distinction – a demonstration of her academic prowess as well as unequalled knowledge of international pharmacovigilance.

As Deputy Director, she is in charge of *the* UMC's overall administration and support services, which includes IT systems planning and development.

She, too, has a rich and varied life outside work, bringing her thorough, methodical approach to sailing and navigation in Swedish waters; to reading and writing; to music and music-making; to the practical enjoyment of rural life at her summerhouse; to generous hospitality, to her family – and her cats.

While Marie Lindquist has contributed substantially to the growth and development of *the* UMC in her own right, much less would have happened if she had not been around to make real the vision and priorities of the Director and of the organisation as a whole.

Lars Magnusson: General Manager, Products and Services

Lars Magnusson leads the team responsible for generating the funds which support the entire UMC operation.

He has a background in electronic technology – university teaching, extensive business activity and management in the sector. He took part in the start-up or development of a number of IT companies. As managing director of Enea Business Systems he saw through the development of the Janus programme, commissioned by the Stockholm Healthcare authorities to provide a range of specialist information to help doctors make more refined clinical and therapeutic decisions.

Later, as a consultant, he worked for *the* UMC helping in the development of the increasingly important areas of product development and sales and marketing, and was later employed to run the division. This move from being a successful consultant was not in the least due to his enthusiasm for the purpose of *the* UMC. He brings his extensive experience of management in the commercial world to *the* UMC, along with a calm, reflective but dynamic personality. He, along with his experienced team, clearly relishes the challenges of managing the extension and improvement of UMC products and services, as well as ensuring the future financial security of the whole operation.

Like others in *the* UMC team, Lars Magnusson is something of a perfectionist. This applies equally to his life outside work where he is an accomplished musician (oboe and vocal) and a keen sportsman. He's also involved in the management of musical activities and music publishing.

Getting things done

While the leadership of *the* UMC rests with the three senior staff introduced here, the primary activities of the operation are managed by a team of 9 managers, responsible for external affairs, traditional medicines, safety reporting services and systems development, research, signal detection and analysis, business and product development, sales and marketing, , finance and administration. A further 35 specialists (including pharmacists, systems developers and programming experts, sales and marketing personnel, liaison and customer support staff, and administrative and IT team support) keep the operation forging ahead from day to day. (They are all listed on the back cover of Uppsala Reports.) Dedicated staff are responsible for supporting the WHO Programme and its member countries.

The Director reports to a formally constituted Board appointed by WHO and the Swedish Government.

the UMC – key dates

1968 WHO Programme established. International ADR terminology and drug dictionary
1969 Definition of ADR
1978 Operations transferred to *the* UMC; setting-up of relational ADR database Regular WHO Programme member meetings
1981 Computerised version of WHO Drug Dictionary available to all
1982 ATC classification coding of all medicinal products
1985 International expert review panel created
1991 On-line WHO database search programme available to national centres
1991 Definitions of adverse event, side effect and causality assessment terms
1993 Windows-based client server program for on-line database searches
1993 Regular training and educational activities
1994 Methodology for use of denominator data for calculation of ADR reporting rates
1997 Knowledge-detection tool for automated signal detection (BCPNN)
1997 Promotion of communication as a necessary discipline
1998 Internet discussion group for national centres
2001 Start of Vigibase Online project
2002 New database system (Vigibase)
2003 New Drug Dictionary with expanded data fields; agreement with IMS Health to increase information in DD
2004 Pattern recognition using the BCPNN on health databases to find safety information.

For a full history of the UMC and the WHO Programme, see Viewpoint 2

Keynote speakers in Messina

Natale D'Alessandro (Sicilian Regional Centre for information on ADRs in Oncology)

Giuseppe Altavilla (Italian Medical Oncology Association)

Oncolytic drugs

Since its foundation, just a few years ago, the Sicilian Regional Pharmacovigilance Centre has been remarkably active and successful. Staff members including Giovanni Polimeni and Francesco Salvo have featured as speakers at international meetings such as those of ISoP and EACPT (European Association for Clinical Pharmacology & Therapeutics). The Centre is well-embedded in the Dipartimento Clinico-Sperimentale of Messina University, directed by Professor Achille Caputi (http://poli.unime.it/dipartim/medfarmacol/index.htm).

Last June a scientific committee composed of Professors Giuseppe Altavilla, Achille Caputi and Natale D'Alessandro organised a pharmacovigilance seminar devoted to a matter of great current interest, the pharmacovigilance of novel oncolytic drugs. A joint initiative of the Faculty of Medicine at the University of Messina, the Sicilian branch of the Italian Medical Oncology Association and the regional health department in Sicily, the event took place in the prestigious Aula Magna of Messina University.

New drugs, new mechanisms

Professor Romano Danesi (University of Pisa) highlighted the recent progress in the understanding of the complex pathology of malignant diseases, which in turn is leading the way to a variety of new lines of selective and effective oncolytic drugs. He talked in detail about Cyclin-dependent kinase inhibitors, Aurora inhibitors, Mitogen-activated kinase kinase inhibitors, protein prenylation inhibitors, growth factor receptor inhibitors and agents that block oncoproteins. Exactly because these drugs have new mechanisms of action, there is still much to be learned about their possible adverse effects and after their introduction intensive safety evaluation is needed.

Quality and quantity of life

Professor D'Alessandro (University of Palermo) reviewed the principles of pharmacovigilance with special reference to cancer patients. He underlined the simultaneous importance of the effects of the treatment on the quantity as well as on the quality of life. Side effects such as anorexia or diarrhoea may not be life-threatening and not serious according to established criteria, but can nevertheless be detrimental to the so-important last part of a person's life. Prof D'Alessandro also showed that, although still small in number, the Messina Regional Centre has received a series of interesting case reports on a variety of oncolytics, including paclitaxel, rifuximab, pegfilgastrin, doxorubicin and mitomycin.

Oncolytic drugs and pharmacovigilance

Dr Ronald Meyboom (UMC and Utrecht Institute of Pharmaceutical Sciences) addressed the challenges to the evaluation of oncolytic drugs and regimens, from the perspectives of both national and international pharmacovigilance. In the past, oncolytic drugs have not been much of a priority to national pharmacovigilance centres and there has not been a reporting culture amongst oncologists. More recently, however, novel oncolytic drugs (together with monoclonal antibodies and antiretrovirals) have become increasingly prominent in the signal detection system at *the* UMC. Dr Meyboom painted an exceedingly complex situation in the development, evaluation and financing of innovative oncolytic drugs and treatments. He came forward with a number of strong recommendations with regard to research, regulation and evaluation, needed to ensure future progress, safety and affordability in cancer treatment.

The well-attended seminar ended with a lively round-table discussion.

EACPT in Poznań

The 7th International Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT) was held in a sunny and warm Poznań, western Poland at the end of June, with participants from academia, industry, health care and regulatory agencies from many European countries.

A packed programme

The conference venue, the Poznań International Fair, boasted a magnificent art exhibition and the Congress President Alexander Mrozikiewicz welcomed all delegates at an opening ceremony accompanied by

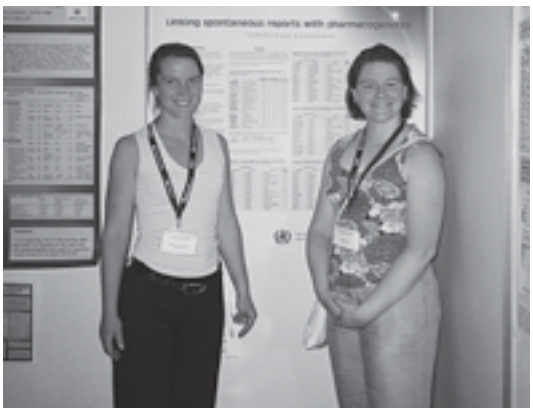
An attractive corner of old Poznań

choral music. The four conference days were filled with interesting symposia and posters[1] where pharmacovigilance, pharmacogenomics, pharmacoeconomics, drug utilization and delivery and the latest in the therapy of obesity, HIV, cardiovascular, rheumatic and neurodegenerative diseases, were discussed.

Synonyms work presented

During the 'Clinical pharmacology and herbal medicine' session Mohamed Farah from *the* UMC presented and discussed the key issues within herbal

adverse drug reactions (ADRs). His principal message was that misunderstandings in the pharmacovigilance of therapeutic herbs can be avoided, by using the correct accepted scientific botanical name instead of local or 'common' names. The publication of 'Accepted scientific names of therapeutic plants and their synonyms' by *the* UMC in collaboration with Royal Botanic Gardens of Kew, UK and the Department of Systematic Botany Uppsala University, Sweden[2] is a step towards this goal. There is a great need of better recognition of herbals as a cause of serious ADRs.



Johanna Strandell and Anne Kiuru in front of the UMC signal poster in Poznań

CYP information and spontaneous reports

Posters on a signal (allergic reactions reported with Cimicifuga racemosa L. Nutt), and on how to improve the signal detection process at UMC by using information on drugs affecting the CYP450 system, were presented by Anne Kiuru and Johanna Strandell. Vigibase contains only 0.7% of reports with drugs reported as 'interacting'. Since the incidence of prescribing drugs with potential for interactions has been estimated to be approximately 5%[3], it is clear that the individual reporter does not normally specify interactions as a possible cause of an ADR, not even for ADRs that are known to be associated with interacting drugs. By combining the CYP information and spontaneous reports the chance of identifying possible drug interactions in Vigibase is increased. *(See page 14 for more.)*

Joint session with ISoP

In the pharmacovigilance session, a symposium run in association with the International Society of Pharmacovigilance (ISoP), chaired by Dr Giampaolo Velo, Dr Nicholas Moore and Dr Michael Orme, the important role of regional pharmacovigilance centres was examined in depth. The use of voluntary ADR reports as a quality indicator was presented in a session chaired by Dr Ulf Bergman, along with quality indicators for drug therapy and in prescribing.

References

1. Proceedings of the 7th Congress of the European Association of Clinical Pharmacology and Therapeutics (2005) Basic Clinical Pharmacology and Toxicology, Volume 97, Supplement I
2. For more information on 'Accepted botanical names and their synonyms', please contact info@who-umc.org.
3. Speight TM, Holford NHG, editors. Avery's Drug Treatment, 4th edition Auckland: Adis International Ltd, 1997.

UMC and FIP embrace patient safety

The International Pharmaceutical Federation (FIP) held its 65th Annual World Congress in Cairo, Egypt 3 – 8 September, 2005. The annual congress was for the first time preceded by a two day workshop on 'Information, Pharmacovigilance and Patient Safety'. This workshop was sponsored by the FIP Pharmacy Information Section, the Pharmacoepidemiology Special Interest Group and the UMC. The main organizer was Keith Johnson, Management Sciences for Health, USA and the session leaders were Graeme Vernon, Australia, Carlos Vidotti, Brazil, Alex Dodoo, Ghana, Bert Leufkens, the Netherlands and Sten Olsson, the UMC.

The enthusiastic workshop speakers and participants in Cairo

Intense workshop discussions

The workshop was attended by about 20 participants from 15 countries, mainly African and Asian. The varied background and perspectives of participants enriched the discussions. Presentations ranged from definitions and basic concepts in pharmacovigilance to pharmacoepidemiology, benefit/harm assessments, regulatory decision-making and risk communication. The roles of healthcare professionals in different positions in ensuring the safety of patients were considered and the need for good communication between partners highlighted. Although the aim of the organizers was to also cover the problem of medication errors and their impact on patient safety, there was too little time to properly discuss this vast area.

Re-visiting the topic next year

FIP plans to repeat the patient safety workshop at future annual congresses. The next occasion will be in Salvador, Brazil, 25 – 26 August, 2006. From a UMC perspective it is very fruitful to collaborate with the international federation as pharmacists have a crucial role to play around the world in safeguarding quality of care and patient safety.

Consumer ADR reporting – alive and well in Australia

Since early 2000, members of Australian public have been able to report adverse drug reactions (ADRs) via a pilot telephone helpline known as the Consumer Adverse Medicine Events (AME) Line.

In 2000, the Australian Government, with support of all Australian Health Ministers, established the Australian Council for Safety and Quality in Health Care (the 'Council') to lead improvements in the safety and quality of care for all Australians.

The AME Line details in the form of a fridge magnet

The Council acknowledged that adverse drug reactions (ADRs) and medication errors are a major source of patient harm and funded the Adverse Medicine Events (AME) Line as a pilot project. This project provided a national phone-in service for the cost of a local call for members of the general public to report concerns with medication safety or suspected ADRs. Hours of operation were Monday to Friday 9:00am to 6:00pm AEST (Australian Eastern Standard Time). Internet access has also been available at www.mater.org.au/ame/. The AME Line pilot service is operated by clinical pharmacists specialising in drug information.

The aims of the pilot service were to:

- provide a system for consumers to directly report their adverse experiences with medicines;
- encourage consumers to report adverse medicine events;
- promote openness and accuracy of information about adverse medicine events;
- identify areas and trends in adverse medicine events to know when, where and how things go wrong; and ultimately
- integrate such information into health systems to improve their safety and quality.

As of 17 June 2005, **the AME Line had received 3,023 calls. Of these 2,781 calls have passed through quarantine** and are described below:

- 44.8% were generated via media publicity, with newspaper articles prompting a fifth of all calls. Over this period, an increasing number of calls (34.6%) were prompted by referral from health professionals, other call centres, consumer support organisations or word of mouth.
- The mean call duration per enquiry was 24 minutes.
- The majority (93.9%) of calls were made by consumers, the remainder by a range of health professionals.
- The ratio of female to male callers was approximately 3:1. This parallels similar caller-gender statistics from a wide range of health call centres.
- Approximately 80% of calls related to the callers themselves. In the remaining 20% of calls, the patient was most frequently the caller's spouse, child or client.
- The 55-plus age group most commonly used the AME Line, representing 62.7% of callers.

Gabriella McConnell answering the AME Line.

In Australia, adverse drug reactions are reported to the Adverse Drug Reactions Advisory Committee (ADRAC), a subcommittee of the Australian drug regulatory agency the Therapeutic Goods Administration. Most reporting to ADRAC is done by health professionals (mostly doctors and pharmacists) and by pharmaceutical companies. Consumers can report through this mechanism however they are not strongly encouraged to do so.

The AME Line received 726 calls from consumers relating to adverse medicine events (AMEs) that met pre-specified criteria for reporting. From these calls, 552 ADR reports were submitted to ADRAC and 174 AMEs (medication error and quality issues) reported to the Council. Overall:

- Approximately 1 in 2 calls (48.4%) involved symptoms that were ultimately judged likely to be medicine-related.
- Approximately one third (28.8%) of calls involved an ADR that did not satisfy ADRAC reporting criteria.
- Approximately 1 in 5 calls (19.6%) resulted in an ADR report to ADRAC.

These data suggested that consumers provided a valuable and reasonably reliable resource for identifying possible medication-related adverse events. In addition, the AME Line pilot provided a useful triaging function for deciding which possible adverse drug reaction should be reported.

	N*	% of sequelae (n=1037)	% of ADRAC reports (n=552)
Dr Consult	316	30.5	57.2
Decreased Quality of Life	247	23.8	44.7
Increased Investigation	155	14.9	28.1
Hospitalised	78	7.5	14.1
Treatment required	68	6.6	12.3
Anxiety	61	5.9	11.1
Loss of Productivity	35	3.4	6.3
Self management	28	2.7	5.1
None	27	2.6	4.9
Time and/or expense	17	1.6	3.1
Fatal	4	0.4	0.7
Treatment Delayed	1	0.1	0.2
TOTAL	**1037**	**100.0**	
None	0.0	0	0.0
TOTAL	**1037**	**100.0%**	

Table 1. Sequelae of ADRs reported to AME Line by consumers

Among the ADRAC reports:

- the most common drugs implicated were atorvastatin, simvastatin, tramadol, mirtazapine, zolpidem, celecoxib, paroxetine and complementary medicines;
- 19.9% of complaints reported were not already listed in the manufacturer's product information;
- in 63.6% of reports the level of causality was probable or certain; and
- approximately 6% of all adverse drug reactions related to complementary and non-prescription medicines.

Table 1 outlines the consequences of all adverse drug reaction reported to ADRAC. Because more than one consequence could be assigned to a single adverse drug reaction, there were 1,037 sequelae described for the 552 ADRAC reports. These sequelae demonstrate that consumers can and do report serious adverse drug reaction that have a significant impact on quality of life.

Complementary medicines

Over the two years of project it has become apparent that consumers provide a rich source of ADR reports associated with complementary and non-prescription medicines. *Table 2* describes ADRs submitted to ADRAC during the AME Line pilot project involving complementary medicines, as well as the ADR term assigned to the reaction. 'Complementary /herbal' preparations refer to those remedies that contained multiple ingredients, where no specific ingredient could be identified as more likely to have caused the ADR.

Medicine	Reaction	No. of reports
Calcium	Oesophagitis, drug interaction, depression	3
Celandine	Hepatitis	1
Chromium picolinate	Allergic reaction	1
Collagen ("Restalyne")	Periorbital swelling	1
Colloidal Silver	Argyria with cardiomyopathy	1
Complementary / Herbal Medicine	Psychosis, shortness of breath, "kidney" pain, abdominal pain, headache, ectopic pregnancy	7
Cranberry	Insomnia (decr. response to dothiepin?)	1
Echinacea	Dermatitis, anaphylaxis	2
Fish Oil	Menorrhagia	1
Garlic	Diarrhoea	1
Ganoderma/Reishi mushroom extract	Hepatic dysfunction	1
Gingko biloba	Bruising, headache (x2) , bloodshot eyes, confusion, dizziness, menstrual disorder (x2), hot flushes	9
Glucosamine	Dizziness, abdominal pain, hyperglycaemia (x3) , allergic reaction, pruritis, peripheral oedema	8
Grapefruit/ Naringenin	Menorrhagia (?Drug interaction w/ oral contraceptive), Hypotension (Interaction with amlodipine)	2
Green-lipped mussel extract	Hepatitis	1
"Holdtite" denture glue	Mucosal ulceration	1
Homeopathy	Nausea	1
Horsechestnut	Nausea (severe)	1
Hydroxyethylrutosides	Syncope	1
Kelp	Hypothyroidism	1
Linoleic acid	Seizures	1
Linseed Oil	Menstrual disorder	1
Magnesium	Abdominal pain, irritable bowel syndrome, chest pain	3
Multivitamin	Anaphylaxis	1
Nicotinamide	Tachycardia	1
Noni Juice	Nausea, agitation	2
Policosanol	Elevation of serum lipids. (?interaction with statin)	1
Poppyseed tea	Dyskinesia	1
Pyridoxine	Myalgia	1
Red Clover	Nausea	1
Rosehip	Vomiting	1
Selenium	Excessive Se serum concentration	1
Sunscreen	Bullous rash	1
Swedish bitters	Drug interaction/ confusion	1
Tumeric	Diarrhoea	1
Valerian	Abdominal pain	1
Vitamin A	Squamous cell carcinoma	1
Vitamins, multi	Pain (renal colic?)	1
Zinc	Taste loss	1

Table 2. ADRAC reports with complementary or non-prescriptive medicines

A key learning point from the AME Line has been that consumers report symptoms, not diagnoses. This limitation of consumer- ADR reporting strengthens the role of the health professional as a learned intermediary, to interpret the reported symptoms into a disease process or advise the consumer on the necessity of a diagnosis, before any drug-associated causality can be assigned.
Of the 174 error, near miss or quality reports:

- most common drugs implicated were zolpidem, thyroxine, methotrexate, levonorgestrel, St John's wort, carbamazepine and warfarin, amoxycillin, tramadol, prednisolone / prednisone;
- most common error types were related to prescribing, dispensing, communication and drug administration;
- resulting problems included adverse drug reactions, receiving too much of the correct drug, receiving an inappropriate drug or treatment delay;
- major contributing factors related to miscommunication, Consumer Medicines Information leaflets, labelling, system factors, training issues and inadequate monitoring.

The AME Line team Standing left to right:
Camilla King, Julie Brown, Greg Kyle, Maria Patounas
Seated left to right: Geraldine Moses , Gabriella McConnell

A key difference between consumer-generated and health professional-generated error/ quality reports is that consumers tend to identify a person as the point in the process where things first went wrong, whereas health professionals prefer to focus on process factors, in order to take a no-blame approach to resolving system issues. To address such issues for consumers, this difference in perspective needs to be acknowledged.

In summary, the AME Line pilot has shown that consumers are a valuable source of drug safety data that includes a range of otherwise unreported and often serious suspected ADRs. In addition, they are a rich and relatively untapped source of ADRs relating to complementary and non-prescription medicines.

Geraldine Moses, AME Line Project Officer and Senior pharmacist

Treasure McGuire, AME Line Project Manager

Mater Health Services
South Brisbane. Australia 4101
PH: 61-7- 3840 8591
FAX: 61-7- 3840 1761

Detecting Interactions in WHO database – Using CYP information

This study was performed by Johanna Strandell, Anne Kiuru and Marie Lindquist and presented as a poster at European Association of Clinical Pharmacology and Therapeutics (EACPT) in Poznan, Poland in June 2005.

The incidence of prescribing drugs with potential for interactions has been estimated to be approximately 5%.[1] Therefore we wanted to determine the extent to which potential interactions are reported as such in the WHO Adverse Drug Reaction database, Vigibase, and if information on cytochrome P450 (CYP) enzymes could be used for identifying new possible interactions in the database and thereby enhance the UMC signal detection process.

The drug substance information in Vigibase was linked to information published in the Cytochrome P450 Drug Interaction table, maintained by the division of Clinical Pharmacology, Indiana University, US[2]. For each drug substance we recorded information on CYP activity (substrate, inhibitor or inducer) and enzyme isoform.

To determine the extent to which potential interactions are reported as such we calculated the proportion of reports listing drug role 'interacting' drugs in the whole database. Up to May 2005, 0.7% of the reports in Vigibase listed 'interacting' drugs.

More detailed investigations were also performed for the year 2000; the numbers of reports with unique drug-ADR combinations listing an 'interacting' drug were compared to total number of reports.

Theophylline and moclobemide, both with known CYP activity were proportionally often reported as 'interacting'. We investigated the reporting odds ratio of the dose related/CYP induced ADR (QT prolonged) compared to non dose related/non-CYP induced ADR (rash). As expected, we found that the reporting odds ratio for dose related/CYP induced ADRs were much greater than for non dose related/non-CYP induced ADRs for drugs acting as CYP substrates.

In order to detect new possible interactions the number of reports for all reported drug-drug-ADR combinations with drugs acting as substrates and/or inhibitors on the same CYP isoform, with one CYP drug reported as 'suspected' and 'other' irrespective of reported drug role, were calculated. We found that many combinations are generally accepted, or listed as interactions in the literature[3].

To conclude, the individual reporter does not normally specify interactions as a possible cause of an ADR, not even for ADRs that are known to be associated with interacting drugs. Combining CYP information and spontaneous reports increases the chance of identifying possible drug interactions. Further studies will be done in this area.

References

1. Speight TM, Holford NHG, editors. Avery's Drug Treatment. 4th edition. Auckland: Adis International Ltd, 1997.
2. Flockhardt D, Division of Clinical Pharmacology, Indiana University, United States, CYP P450 Drug Interaction Table. (Accessed in 2004). Url: http://medicine.iupui.edu/flockhart/table.htm
3. The Medicines Compendium, Datapharm Communications Ltd. Electronic Medicine Compendium. Electronic version. (Accessed in May 2005). Url: http:// www.medicines.org.uk/

Top International Award for Researchers

Roland and Niklas in Chicago with their award.

the UMC's specialist data-mining team has won the award for Best Applications Paper at the 11th ACM SIGKDD[1] International Conference in Chicago, USA. This is *the* major, annual global conference on Knowledge Discovery and Data Mining (KDD), involving around 700 specialists from a wide range of disciplines and areas of human activity all over the world.

The paper *'A hit-miss model for duplicate detection in the WHO drug safety database'*, resulting from research by Niklas Norén, Roland Orre (of Neurologic) and Andrew Bate, dealt with an automated method for detecting duplicate entries in very large data sets – a significant problem which, up to now, had been unresolved.

To get reliable results from analysis of around 3.5 million reports in the WHO Drug Safety Database (received from more than 75 countries), the detection of duplicate entries is a critical process. The issue is equally important for government databases, and industrial, commercial, financial and medical applications of all kinds.

Ralph Edwards congratulated the team, saying "While we work in a small – but important – corner of human affairs, our Research and Development team has come up with a solution which is useful in different applications and whose significance has been recognised as first class by a group of leading international experts." Niklas presented the paper at a special session of the conference (in Chicago, August 2005). As well as the kudos of winning, the team also received a prize of US$1,000 between them.

For further information, contact Niklas Norén: niklas.noren@who-umc.org. A copy of the paper is accessible at: www.who-umc.org/ >What's New

ACM (Association for Computing Machinery) was founded in 1947, and seeks to advance the skills of information technology professionals and students worldwide.

Refrerence

1 ACM: Association for Computing Machinery; SIGKDD: Special interest group in Knowledge Discovery and Data Mining

Looking for patterns in the WHO data

A paper was published recently in the International Journal of Neural Systems (IJNS) by the data-mining specialists, entitled 'A Bayesian Recurrent Neural Network for Unsupervised Pattern Recognition in Large Incomplete Data Sets'. The authors were Roland Orre, Andrew Bate, Niklas Norén, Erik Swahn, Stefan Arnborg and Ralph Edwards. With such a long title and so many authors one may ask if there is a simple way to express what was found in the paper?

The neural network (BCPNN) here does something we are ourselves often quite good at, that is to be able to detect patterns in the events we see around us. A syndrome is an example of such a pattern. A drug-induced syndrome, which may be caused by a specific drug or combination of drugs, is composed of several symptoms but despite this we wouldn't expect to find all symptoms of a syndrome in a specific patient.

After taking a specific drug, one patient may get a few symptoms like dystonia and pyrexia, another will have dystonia and coma, and a third patient pyrexia and coma. If we only see these three patients we would not draw any conclusions but if we see several hundred patients with these symptoms, we may suspect that dystonia, coma and pyrexia are part of the same syndrome.

The judgement of whether these symptoms are part of a pattern is calculated by the network from the likelihood that these symptoms should occur together. If the different symptoms are not independent of each other, the neural network will find that it is more likely that these events occur together than they don't.

In the IJNS paper an analysis is made by comparing the neural network performance with a clustering method (autoclass) which was originally developed for analysis of satellite images.

The methods were compared using an artificial example and a real syndrome example from haloperidol data. In Figure 1 you can see two artificial prototype patterns and in Figure 2 you can see the distorted versions of these prototypes presented to the network. The corresponding output from the neural network is shown in Figure 3.

Figure 1

Figure 2

Figure 3

Table 1 lists terms associated with the neuroleptic malignant syndrome as identified when using the network to analyse WHO haloperidol data.

Table 1. ADR terms

Neuroleptic malignant syndrome	Hypertonia
Fever	Tremor
Confusion	Creatinephosphokinase increased
Agitation	Coma
Convulsions	Tachycardia
Stupor	Hypertension
Sweating increased	Dysphagia
Leukocytosis	Urinary incontinence
Apnoea	

The neural network clearly outperformed the clustering method both in speed and performance. Performance-wise the neural network managed noise and incomplete data better. On real haloperidol data the neural network found three of the most well-known syndromes for haloperidol where autoclass found only two patterns of little medical significance.

Yet there exists no simple way to describe what these patterns found by the network actually are, as they may not be caught by a simple formula, but it is understood that the network maximises the likelihood for the items in a pattern to occur together. The patterns are found when the network performs a computation which resembles how information is processed within our own brains; the neural network could therefore be seen as a statistical approach to artificial intelligence.

For Beje Wiholm

Ralph Edwards

To say that Beje will be sorely missed, for me and his many friends and associates, is both a truth and a failure to describe the loss of a complex and delightful, caring, friend and professional.

Memories of Beje whisper insistently in many areas of life and thought. Everything he did was modest and unassuming. Little escaped his notice, evaluation and comment, and to miss his quietly spoken, precise observations was to lose his wisdom, so valuable in many situations. He would often stop you mid-conversation, and say, "Look at that!" or "I know! What do you think of this?". He was often frustrated by his failure to be heard when he wanted, particularly in meetings, but even in anger he kept restraint and objectivity: and he usually found a way of impressing people anyway!

We all know he was superb professionally. He was a careful, progressive and clever pharmacoepidemiologist, one of the leaders in drug safety and in the International Society of Pharmacoepidemiology of which he was a past President. He had a flair and imaginative skill for designing studies to fit practical issues, and for general planning to enable better monitoring of drug safety. His handling of Zimeldine and Guillain-Barre Syndrome cases was an early example of the first skill, and his creation of the devolved Swedish pharmacovigilance system, and the use of nurses to create a rolling control group for case-control studies were amongst many other far-sighted developments in Sweden. He was also quick to incorporate others' good ideas and unfailingly to give credit for them. In an area where disputes over ideas and data seem common, it was always a pleasure to trust his integrity. He was also an epidemiologist who did not show the usual disdain for anecdotes and spontaneous reports of drug concerns. He was able to balance all information available and propose pragmatic solutions to safety problems, based on extensive experience. His professional work had always been focussed towards individual patient care, as much as to public health. It was this humanity that shone through everything he did, motivated him. The combination of his tireless hard work, idealism and a genuine care for people meant that those close to him would always give of their utmost to support him, in spite of the irritations. Why was he always ten minutes late for any meeting?

He could never say "no". His family and those who worked with him had to cope with this trait; not easy when his quiet but insistent expectation was always to do the best. He never stopped trying to do more. It is a great shame that more professional and academic acclaim has not been forthcoming for all Beje's efforts and involvement in key areas of national and international drug safety. I know he was very disappointed by this, but he was generous with his thoughts and ideas, and did not always get credit when it was due. He certainly deserved better, but I was delighted that the Royal College of Physicians of London recognised his work by an honorary Fellowship, a clear mark of international distinction.

It was Beje who gently persuaded me to move to Sweden. It was he who helped smooth the passage for me to enter life in a new country and to become useful. Even with my linguistic limitations, he made it possible for me to work. It was so enjoyable to sit with someone whose knowledge was broad, whose gentle wit was always there to lighten the tougher times, and whose imagination and idealism was a continuing inspiration. Tackling problems was a pleasant task with such a person. We already had common ground concerning the need to be able to move from reported suspicions of drug safety to harder data, and Beje was very interested in the New Zealand Intensive Medicines Monitoring Programme, and the ways we developed and utilized cohorts. It was also Beje who proposed that he in Sweden, and I from New Zealand, should join forces to persuade the Council of International Organizations of Medical Sciences (CIOMS) to work on what was to later become Periodic Safety Update Reporting by industry (several others have taken credit for that development!).

But it is not the professional Beje that needs to be dwelt upon, it is the person who counts much more. We also shared interests in art - discovered during several hours of discussion over modern art in the Smithsonian in Washington, and in sailing – many shared anecdotes on the 'art of course sailing' over beers, and in cars - though his was in driving and mine more technical. It is dreadful that his joy from driving should lead to his death, but it seems likely that he was happy in his last moments.

Not all has been plain sailing: the pressures put upon Beje by others, and himself, had to cause some problems. Those problems ultimately led to his leaving Sweden and going to the United States where he set about putting his personal and professional life together again in a very courageous way. I will always wish I could have helped him more during that time, just as I wish that I could enjoy Beje for longer now.

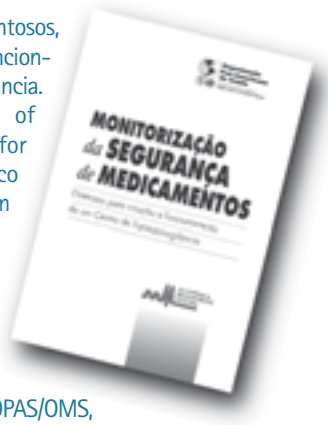
There will never be enough time for someone like Beje. There was always too much to be done, too many dreams to be realised and too many promises to be fulfilled. But we have all been cheated by his accident; no time even to say "Goodbye", but on the other hand a miscellany of memories of a genuine and important human being whose work and personality will never be forgotten. This is so much more relevant to his family, and our thoughts must be with them as they mourn the loss of a person who felt so much for them.

Beje, I will always think of you as the person with the 'butterfly effect': the many gentle ripples that you have created have already had profound and positive effects, in many ways and on many people. They will not go away.

Segurança dos Medicamentos – four new Portuguese translations

Nelly Marin, Co-ordinator of Medicines and Health Technologies at the PAHO/WHO (Pan American Health Organization) in Brazil has informed Uppsala Reports about an important educational initiative for countries where Portuguese is an official language.

Under a co-operation agreement between PAHO/WHO and the National Health Surveillance Agency (ANVISA), Ministry of Health, Brazil, publication is taking place of several UMC / WHO publications, translated into Portuguese.



Segurança dos produtos medicamentosos, diretrizes para o planejamento e funcionamento de um centro de Farmaco-vigilância. (Original title: Safety Monitoring of Medicinal products, guidelines for setting up and running a Pharmaco vigilance Centre). Downloadable from http://www.opas.org.br/medicamentos/ docs/HSEMON _SEG_0305.pdf

Segurança dos Medicamentos: um guia para detectar e notificar reações adversas a medicamentos. Brasília: OPAS/OMS, 2005. (Original title: Safety of Medicines - a guide to detecting and reporting adverse drug reactions [WHO/EDM/QSM/2002.2]) Downloadable from http://www.opas.org.br/medicamentos/docs/HSE_SME_0105.pdf

A Importância da Farmacovigilância. Brasília: OPAS/OMS, 2005. (Original title: The Importance of Pharmacovigilance: Safety monitoring of medicinal products) Downloadable from http://www.opas.org.br/medicamentos/docs/HSE_IMP_FAR_0305.pdf

Medicamentos falsificados: diretrizes para o desenvolvimento de medidas de combate a medicamentos falsificados. Brasília: OPAS/OMS; 2005. (Original title: Counterfeit drugs: Guidelines for the development of measures to combat counterfeit drugs).Downloadable from http://www.opas.org.br/medicamentos/docs/HSE_MED_FAL_0305.pdf

ANVISA will be sending copies to Portuguese-speaking countries. It is hoped that other key pharmacovigilance texts will also be translated via this initiative in the near future.

A Portuguese translation of the 'Erice Declaration' translation is currently available at this site: http://www.sobravime.org.br/direito_declaracao_erice.html

Bonnes Pratiques de Pharmacovigilance

We would also bring to the attention of readers an updated 'Bonnes Pratiques de Pharmacovigilance' produced by the French national centre AFSSAPS (Agence française de sécurité sanitaire des produits de santé). This is downloadable from their website (www.agmed.sante.gouv.fr/pdf/5/5010.pdf) and while geared towards regulatory activity in France and the EU contains some useful information for the wider francophone audience.

Safety Monitoring in Italian

Safety Monitoring of Medicinal Products (Guidelines for setting-up a pharmacovigilance centre) is being published in Italian, through a collaboration with the Sezione di Farmacologia, Dipartimento di Medicina e Farmacologia (pharmacovigilance section of the medicine and pharmacology department) at the Policlinico Universitario di Messina. The Italian Society of Pharmacology is supporting the costs of printing the books. Giovanni Polimeni of the Messina centre has co-ordinated this project.

UMC website gets a face lift

The design and layout of the Uppsala Monitoring Centre website has remained the same for some time, although it has increased greatly in the amount of information available to read and download. However, the opportunity recently arose to recreate the site at minimal cost. The site will soon look different, but more importantly will be restructured to take account of changes in the way the UMC's work has developed in the intervening years.

The main sections of the website will become:

- WHO Programme
- About the UMC
- UMC Activities
- Practical Pharmacovigilance
- Publications
- Meetings
- Promotion and Training
- FAQs
- Links

Practical Pharmacovigilance is a new section based mainly on what was previously 'Definitions'. This was felt to be too narrow a title, so we have changed it and added more material of a 'practical' nature for pharmacovigilantes. Following the initial transfer of the site, other changes will be notified in future Uppsala Reports.

Material in the old 'Products & Services' section has for a year now been incorporated in the www.umc-products.com site, but 'permanent' information on the WHO Drug Dictionary and WHO-ART will be also available from the main UMC site.

We hope that colleagues and friends will encourage their organisations to link their websites to the UMC's as a vital source for additional information. We also welcome any comments on or criticisms of the UMC website. Please send them to geoffrey.bowring@who-umc.org

African Countries: Regulatory training in Madrid

On 6-10 June 2005 an advanced seminar on 'Strengthening of Medicine Regulatory Authorities' was held in the National School of Health in Madrid, coordinated by the Spanish Agency of Medicines and Health Products (SAMHP); 20 health professionals from different African countries attended. This seminar formed part of the VITA Program (www.aeci.es/vita), promoted by the Spanish International Cooperation Agency (AECI), as an Enhancement of National Health Care Systems. It contributes to the attainment of the Millennium Development Goals (Target 17), in improving access to medicines, at appropriate prices, in populations with fewer resources in the health field in Africa.

The closing ceremony: Mrs Consuelo Ondo Efua Mangue (Director General of the National Centre for Essential Medicines, Equatorial Guinea) offers thanks on behalf of all participants

The seminar was coordinated by the SAMHP in collaboration with the 'Carlos III Foundation for International Health and Cooperation'. The 5 days consisted of theoretical classes, the resolution of practical cases, workshops and technical visits to the National Control Laboratories in Majadahonda. The programme included: national pharmaceutical policy, rational use of medicines, national reference laboratory, inspections, the risk-benefit balance, spontaneous reporting, yellow card systems, WHO International Programme, risk management,

Participants after the farewell drinks

observational studies, and pharmacoepidemiology. Dr Francisco J de Abajo and Mariano Madurga of the Division of Pharmacoepidemiology and Pharmacovigilance of the SAMHP were the teachers for these last items.

The 20 health professionals are directly involved in medicine management, with responsibility in national and local health systems: Daniel Antonio and Andre Pedro Neto (Angola); Edith Mauricio Dos Santos and Ana Filomena Soares de Cruz (Cape Verde); Consuelo Ondo Efua Mangue and Rafael Mocong Mate (Equatorial Guinea); Abraham Gebregi Kahsay (Ethiopia); Samuel Boateng and Felix Yellu (Ghana); Pepas Vicente Natak and Zeferina Gomez da Costa (Guinea Bissau); Alexandre Louren Manguille and Samuel Patel (Mozambique); Lazarus Mwashek Indongo and Johannes Gaeseb (Namibia); Dora Knem Akunyili, Edosa Ogbeide and Barbara Otito Emeter (Nigeria); Marcelina Quares J da Costa and Madalena Afonso Lopes da Silva (Sao Tomé and Principe).

China and UMC collaborate

In early 2005 the UMC received a unique request from the drug control authority of China (SFDA) to run a one-week pharmacovigilance training course in Uppsala for managers of the Chinese pharmacovigilance network. The Chinese authorities are putting a major effort into building a network for pharmacovigilance involving all 31 provinces and several representatives of the network have already attended the two-week courses at *the* UMC over the years. After an extended exchange of messages we agreed on which parts of the general course should be included in and adapted to the specific training for the Chinese programme. With some difficulty *the* UMC managed to squeeze this training in a busy September schedule, and a delegation of 22 from different provinces of China spent the week of 12–16 September in Uppsala. In spite of the fact that all lectures and discussions had to be translated between Chinese and English we had very interesting and fruitful interactions between course participants and UMC staff members. The positive experience of this joint training could lead to a repetition of the adapted UMC course in 2006.

If other countries are contemplating using UMC experience in providing tailor-made pharmacovigilance training we should emphasize that a

The 22 Chinese course participants pose during a break in Uppsala

proper planning period is essential. UMC involvement in training activities are normally planned during October – November for the coming year, and our availability for training, sadly, is limited.

All Countries Need Pharmacovigilance

Alex Dodoo reports

The importance of pharmacovigilance systems in resource-constrained developing countries has again been stressed at a major conference on access to medicines. Participants at the June 2005 'Strategies for Enhancing Access to Medicines' (SEAM) conference in Accra, Ghana called on governments, policy makers and the donor community to ensure that global initiatives towards enhancing access to medicines are accompanied by an equally active and passionate effort to establish systems to monitor the safety of the deployed medicines. Ralph Edwards, Director of *the* UMC, stressed the importance of ensuring that wide-scale deployment of life-saving medicines is accompanied by robust, locally-relevant monitoring systems to ensure safe and rational use. This in turn will help prevent non-adherence to treatment and the development of resistant strains.

The conference, whose theme was 'Targeting Improved Access', devoted a half-day parallel session to pharmacovigilance. Experts from Africa, Asia and Europe contributed enthusiastically in the well-attended session. The role of pharmacovigilance in enhancing public health programmes was exemplified by Ghana, where a simplified reporting system for women on anti-malarial prophylaxis has strengthened national malaria policy.

Counterfeiting of drugs and its negative impact on patient safety was graphically described by Dr Dora Akunyili, Director-General of the National Agency for Food and Drugs Administration and Control, Nigeria, whose account of the dangers of counterfeiting included a demonstration of tricks used by counterfeiters. She called for a global anti-counterfeiting convention to deal with the threat.

Dr Mohan Joshi (USA) discussed anti-microbial resistance and described strategies that countries could utilise to contain the problem. In an interesting discussion, Mr J B Annan of the Central Medical Stores, Ministry of Health, Ghana, spoke about the role of portable digital assistants (PDAs) in resource-poor settings to improve drug supply management – as well as to collect and transmit information on adverse drug reactions to national pharmacovigilance centres. The falling costs of PDAs, and the availability of useful reference material on drugs generally and specifically management of drug toxicity, makes the prospect of using PDAs realistic and appealing.

Ralph Edwards, Dora Akunyili and Alex Dodoo take questions at the SEAM meeting

Demonstrating the methods of couriers of counterfeit medicines: a typical small haul for enforcement authorities

Clinical pharmacy is quite a new concept in many developing countries; Mrs F Nkansah, Principal Clinical Pharmacist in charge of the Surgical Department Pharmacy at the 1,600-bed Korle-Bu Teaching Hospital in Accra discussed how clinical pharmacists can play a key role in pharmacovigilance. Clinical pharmacists are often good reporters of adverse drug reactions and their access to both clinical and pharmaceutical information of patients makes them key in collecting ADR information. They can also be focal persons for interventions designed to prevent adverse reactions.

A further PhD thesis devoted to pharmacovigilance

The scientific power of national and international pharmacovigilance systems has again been demonstrated in an academic thesis. On 17 September Karin Hedenmalm of the Swedish Medical Products Agency was granted the title Doctor of Philosophy (Medicine) at the University of Uppsala after successfully defending her thesis 'Hazards of Drug Therapy – on the management of adverse drug reactions: from signal detection and evaluation to risk minimization', (ISBN 91 554 6291). (http://publications.uu.se/theses/marc21.xsql?dbid=5866).

Dr Ellen Vinge, Department of Clinical Pharmacology, University of Lund, was the opponent to the thesis. Dr Vinge, a member of the UMC Board, gave an introduction, starting from history with Hippocrates' well-known phrase "Prima non nocere - First do no harm", through the early findings of adverse reactions in the 19th century until today.

Karin Hedenmalm summarized the six works of her thesis, and then followed a thorough discussion of the work between her and Dr Vinge. The six studies were published in major journals, using either the WHO adverse reactions database (Vigibase) or the Swedish national spontaneous reporting system. All studies concerned important safety issues and provided valuable information, substantially improving our knowledge. The 'Vigibase' studies concerned the connection between clinical hyponatriaemia and the use of antidepressant drugs, and glucose intolerance caused by clozapine and other 'atypical' neuroleptics. During the defence, many of the slides presented showed BCPNN graphs, illustrating that the Bayesian method developed by the UMC is being embraced by the wider scientific community.

The national studies also produced valuable information regarding insufficiently known matters, such as peripheral nerve injury due to fluoroquinolones, oral contraception and pulmonary embolism, and involuntary 'extrapyramidal' movements in connection with the use of SSRIs. Karin Hedenmalm's study regarding the controversial analgesic dipyrone (metamizole) revealed an alarmingly high reporting frequency of granulocytopenia and other serious blood dyscrasias, justifying the ban on this drug in many countries around the world. Pharmacovigilance needs bright young scientists like Karin Hedenmalm. Offering the possibility to new staff members of preparing a PhD can be a creative and effective way of keeping such people in our profession, with simultaneous benefits for the person and the centre!

WHO Drug Dictionary Enhanced gets bigger – and new WHO Herbal Dictionary

On June 1, 2005 the first release of the WHO Drug Dictionary Enhanced was distributed. The new dictionary is the result of a collaboration with IMS Health and will make it possible to reach nearly 100% coverage of the products marketed within each country. The increased coverage minimises the need for manual investigations by the end users and reduces the risk of making incorrect assumptions. The first release contained IMS Health data from the United Kingdom, Japan and Finland.

We have just delivered the second release of the WHO Drug Dictionary **Enhanced** with additional data from eastern Europe. This has resulted in the following statistics;

Country	number of Product Names	number of Unique Names	number of Medicinal Products (variation MAH/Form/Strength)
United Kingdom	11,600	8,800	23,900
Finland	5,600	3,900	10,500
Japan	17,900	13,500	35,200
Poland	5,100	3,500	9,600
Latvia	6,500	4,200	11,900
Lithuania	6,200	4,000	11,200
Hungary	2,800	2,100	5,200
Estonia	4,300	2,800	7,800
Czech Republic	3,300	2,200	6,800

WHO Drug Dictionary **Enhanced** is providing:

- Data from more countries
- More data per country
- Fast and frequent updates

WHO Drug Dictionary **Enhanced** - numbers

Type/Format	number of Medicinal Products in C Format	number of Drug records in B.1 Format	number of Drug records in B.2 Format
WHO Drug Dictionary	134,207	114,654	58,859
WHO Drug Dictionary **Enhanced** Including WHO DD	266,109	184,141	80,107

In the next release of the WHO Drug Dictionary Enhanced (December 1st, 2005) the following countries will be updated with IMS data: USA, Mexico, Germany, Austria and Canada. The order by which new countries are implemented is decided together with customers based on the need for increased coverage, because of intensified clinical research in these countries.

Future versions of WHO Drug Dictionary Enhanced will include products from the USA, the European Union and 40 other countries, and more than double the number of entries per country. WHO-DD Enhanced is produced in the same formats and with the same principles as the WHO Drug Dictionary.

ATC hierarchy

The WHO-DD Enhanced contains the WHO's Anatomical Therapeutic Chemical (ATC) classification. The hierarchic classification helps users to aggregate statistics, find patterns in the co-medication and increase understanding of the properties of the drugs.

WHO Herbal Dictionary

The WHO Herbal Dictionary is populated with data from WHO Drug Dictionary as well as additions from other sources.

The products that are included in the WHO Herbal Dictionary contain only substances of natural origin. The WHO Drug Dictionary/WHO Drug Dictionary Enhanced cover the products that contain conventional substances or a combination of conventional substances and natural substances.

The hierarchical record number system allows for easy, flexible information retrieval. Drugs are classified according to the Herbal Anatomical-Therapeutic-Chemical classification (HATC) which allows for grouping of drugs in different ways for comparison purposes. The dictionary also contains cross-references to market authorization holders and reference sources.

The Herbal ATC system is an integral part of the WHO Herbal Dictionary and provides a unique scientific framework for a harmonised, global nomenclature and therapeutic classification of herbal substances and combinations of them. The HATC is based on the ATC classification which is a part of the WHO Drug Dictionary.

The main benefits offered by the WHO Herbal Dictionary are:

- Consistent, quality-assured, and up-to-date information
- A hierarchical structure that allows easy and flexible data-retrieval and analysis at different levels of precision
- Chemical and therapeutic classifications - using the WHO drug record number system and the Herbal ATC classification
- Computerised software-independent format for easy implementation in the user's systems

The WHO Herbal Dictionary is produced twice per year – on March 1 and September 1 each year. The March 1 version contains the new revision of the Herbal ATC classification.

Current data in the WHO Herbal Dictionary:

Type/Format	# of Medicinal Products in C Format	# of Drug records in B.1 Format	# of Drug records in B.2 Format
WHO Herbal Dictionary	5,251	4,423	2,603

It is possible to subscribe to the WHO Herbal Dictionary separately or combined with the WHO Drug Dictionary or the WHO Drug Dictionary Enhanced. These combined dictionaries are available on the same dates as the WHO Herbal Dictionary.

The optimal solution for coding co-medication is the combined WHO Drug Dictionary Enhanced and WHO Herbal Dictionary. This combination makes the coding straight forward since the combined dictionary contains a very high percentage of all drug names in the world. This reduces the need for manual investigations, increases the quality of the coded data and makes it possible to analyse all types of products using the combined ATC/Herbal ATC.

Support

As a subscriber to the WHO Herbal Dictionary you will have full access to UMC support services. Support will help you to interpret documents and files. You should also report any errors or inconsistency to Support so we can solve the problem. Support is staffed during European office hours.

User Group Portal

The User Group Portal on the WHO Drug Dictionary customer website assists both new customers and experienced users. The portal contains a library of articles and documents related to the User Group, advertises forthcoming User Group Meetings and has a discussion forum. We hope you will find this a useful way to keep up-to-date with WHO Drug Dictionary developments (you will need a password to register).

User Group meetings

During recent months there have been two WHO Drug Dictionary User Group meetings in Lisbon, Portugal and Arlington, USA. 20 User Group members gathered on each occasion to discuss WHO-DD matters. The first part of the meeting was dedicated to the introduction of the two new dictionaries, the WHO-DD Enhanced and the WHO Herbal Dictionary.

Buying UMC services online

the UMC's Products and Services website is able to process the majority of orders for UMC services and products via the 'web shop'. When placing an order in the web shop, you can also calculate the cost and, where appropriate, generate a standard licence agreement. www.umc-products.com.

Get the price list

The new price list valid from 1st May 2005 - 2006 is available. If you are interested in obtaining a copy, please download from our website.

1st September 2005 versions

The new versions of the computerised WHO-DD, WHO-DD Enhanced and WHO Adverse Reaction Terminology (WHO-ART), containing information collected up to the 30th 2005 are now available. The WHO-ART version is 2nd quarter 2005. Updates were sent to subscribers during June 2005. The WHO-DD pack contained the updated version of WHO-DD, as well as a range of technical material.

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 the UMC Products & Services.
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.

If you are a subscriber and have not yet received your update, please contact Katarina Hansson.

The next versions of the drug dictionaries should be available for web customers to download on December 1, 2005.

Great interest at the launch of the WHO Herbal Drug Dictionary

House of Representatives visitors

the Uppsala Monitoring Centre were delighted to welcome Kelli Andrews and David Nelson from the US House of Representatives Committee on Energy and Commerce on 22 and 23 August.

The Committee on Energy & Commerce of the United States House of Representatives has responsibility for public health issues generally, and specific oversight authority for USA regulatory agencies, including the Food & Drug Administration (FDA). The Committee has conducted several investigations into various aspects of drug safety issues, and considers whether changes in laws may be necessary, following these inquiries. Members of the Committee decided to learn about the methods that other non-US regulatory bodies are using to address both drug safety issues generally, and issues that have arisen with regard to certain drugs and/or classes of drugs.

Kelli Andrews and David Nelson in Stadsträdgården, Uppsala

The two visitors had discussions with UMC staff on:

1 the development of the WHO's international drug adverse event reporting system
2 analyses or recommendations surrounding the following drugs/classes of drugs: (a) selective Cox-2 inhibitor drugs and NSAIDs; (b) SSRI's/suicidality issues; (c) Isotretinoin, that were done in connection with data-mining efforts at *the* UMC;
3 discussion of how to improve data-mining of adverse event reporting in post-market environment.

In addition to Ralph Edwards, Marie Lindquist and Sten Olsson, other UMC staff members presented UMC and WHO Programme work. Members of the data-mining team were at conferences in Nashville and Chicago that very week, however, responses to questions about where we are heading with our data-mining methodology, its strengths and weaknesses were discussed.

Renan Bonnel of the FDA, who spent a month working at *the* UMC last year (see UR28 p16), had suggested that Ms Andrews and Mr Nelson contact *the* UMC to arrange the visit.

Japanese delegation

Three representatives from the Japanese government department responsible for drug safety spent two days at *the* UMC at the end of August learning more about our work. The delegation consisted of Masahiko Yokota, Director, Drug Safety Division, Pharmaceutical and Medical Devices Agency (PMDA), Tokyo and Satoru Nakamura, Professional Officer, Safety Information Division, PMDA, along with Dr Masahiro Terabe, Safety Engineering and Technology Department, Mitsubishi Research Institute, Tokyo.

Marie Lindquist, Masahiko Yokota, Satoru Nakamura, Masahiro Terabe and Ron Meyboom on a bridge over the Fyris in Uppsala

After having been greeted by Sten Olsson and Ron Meyboom, the first day was devoted to presentations on signal detection and data-mining methodology. Signal detection methods, operating systems and use of data-mining were viewed in more depth. Discussions also continued at a traditional Swedish restaurant in the evening. The second day examined the issues around submission of ADR reports from Japan to the WHO database with Marie Lindquist and Jessica Nilsson. Andrew Bate spoke about pattern recognition. Data quality and quality management were discussed alongside documentation grading and duplicate detection.

It is expected that the report submission interval from Japan will be three times per year in future and in addition that the body of industry reports from Japan can be submitted at a future date.

Panamanian programme

Hildaura Acosta de Patiño

Dr Hildaura Acosta de Patiño from the Department of Pharmacology, Faculty of Medicine, University of Panama visited the UMC on 23 August. She is involved both in the Panamanian programme on occupational health and in the pharmacovigilance programme that was initiated in 2001 by Ministry of Health. During her short stay in Uppsala Hildaura de Patiño presented the present position of pharmacovigilance in Panama and demonstrated the designated web site established by the programme. She discussed with Sten Olsson of the UMC how pharma-covigilance in Panama can become more closely integrated with the international pharmacovigilance community and the WHO Programme in particular.

Vellore Visitor

Dr Sujith Chandy from the Christian Medical College in Vellore, India, visited the UMC on 17 September. His college has, particularly from an Indian perspective, a long history in pharmacovigilance. Adverse reaction reporting routines were introduced there already in the 1970s by the late Dr Molly Thomas. Dr Chandy had met Sten Olsson at the training course for the new Indian pharmacovigilance network that was held in Mumbai, January 2005. He had now been invited to Uppsala for a summit on bacterial resistance to antibiotics and also took the opportunity to visit the UMC.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
7-8 November 2005	Pharmacovigilance Specifications and Risk Management	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
13-15 November 2005	Annual Conference, Society of Pharmacovigilance, India	Ahmedabad, India	SoPI Fax: +91 56 222 303 12 E-mail: sandeepcancer@rediffmail.com
16 November 2005	Pharmacovigilance aspects of licensing agreements	London, UK	Management Forum Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 E-mail: info@management-forum.co.uk www.management-forum.co.uk
16-17 November 2005	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
22-23 November 2005	Leading-edge strategies and technologies for effective pharmacovigilance, risk management and post-marketing studies	Amsterdam, Netherlands	eyeforpharma Tel: +44 20 7375 7575 E-mail: iwakeling@eyeforpharma.com www.eyeforpharma.com/rxsafety
28 November 2005	Data Safety Monitoring Boards	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
28-29 November 2005	1st Annual DIA Cardiac Safety Conference	Vienna, Austria	DIA Tel: +41 61 225 51 54 Fax: +41 61 225 51 52 E-mail: phyllis.suter@diaeurope.org
12-14 December 2005	Basic course on pharmacovigilance	London, UK	Management Forum Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 E-mail: info@management-forum.co.uk www.management-forum.co.uk
1-3 February 2006	Medical Aspects of Adverse Drug Reactions	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
22-23 February 2006	Monitoring Safety in Clinical Drug Development	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
6-8 March 2006	18th Annual EuroMeeting	Paris, France	DIA Tel: +41 61 225 51 51 Fax : +41 61 225 51 52 www.diahome.org
30-31 March 2006	VI Jornadas de Farmacovigilancia	Madrid, Spain	Reg. Cent. of Community of Madrid & Spanish Medicines Agency Tel: +34 91 204 2600 Fax: +34 91 559 7411 E-mail: dccimad6@viajeseci.es www.jfv2006.com
27-28 April 2006	A 2-day international symposium on Pharmacovigilance of herbal medicines: Current state and future directions	London, UK	Ms Judy Callanan, Conference Secretariat Royal Pharmaceutical Society Tel: +44 (0) 20 7572 2261 Fax: +44 (0) 20 7572 2506 E-mail: science@rpsgb.org.uk www.rpsgb.org/science
24-25 April 2006	International Society for Pharmacoepidemiology (ISPE) Mid-Year Meeting	Rockville, Maryland, USA	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
26-27 April 2006	Back to Basics in Pharmacovigilance 22nd International Conference on Pharmacoepidemiology & Therapeutic	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
24-27 August 2006	Risk Management	Lisbon, Portugal	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com

the Uppsala Team

Director
Ralph Edwards, MB, ChB, FRCP (Lond), FRACP **Professor in Medicine, Director**

Executive Group
Marie Lindquist, Dr Med Sc **Deputy Director, General Manager, Science & Technology**
Lars Magnusson **General Manager, Products & Services**

Administration
Marjatta Leván, BA **Manager**
Cecilia Biriell, MSc Pharm **Senior Specialist, Head of Internal Affairs**
Ali Bahceci **Network Technician**
Anneli Lennartsson **Economy Assistant**
Linda Wallin **Team Support**

Science and Technology

Safety Reporting Support & Service, and Systems Development
Magnus Wallberg, MSc Eng Phys **Manager**
Bill Dagérus **Senior Systems Developer**
Stefan Lewenfalk **Systems Developer**
Annica Lundström, BSc Pharm **Data Management**
Jessica Nilsson, BSc Pharm **Programme Leader, Data Management**
Helena Sjöström, Pharmacist, **Data Management** *(on maternity leave)*
Bo Östling **Senior Systems Developer**

External Affairs
Sten Olsson, MSc Pharm **Manager, Head of External Affairs**
Geoffrey Bowring, BA **External Affairs Co-ordinator**
Jenny Ericsson, BSc Pharm **Programme Leader, Traditional Medicines**
Mohamed Farah, Pharm D **Senior Specialist, Traditional Medicines**
Helena Fucik, BSc Pharm **Senior Specialist, External Affairs**
Anna Lindquist **Web Editor** *(on study leave)*

Research & Development
Andrew Bate, MA (Oxon), PhD **Manager**
Jonathan Edwards **Programme Leader, Data Mining Development**
Niklas Norén, MSc Eng Phys **Data Mining Research Engineer**
Malin Ståhl, MMedSc **Research & Development**
Erik Swahn, MA **Data Mining Developer**

Signal Detection & Analysis
Monica Plöen, BSc Pharm **Manager**
William Frempong, BSc Pharm **Signal Detection & Analysis**
Anne Kiuru, MSc Pharm **Signal Detection & Analysis**
Kristina Star, Registered Nurse **Signal Detection & Analysis**
Johanna Strandell, MSc Pharm **Signal Detection & Analysis**

Products and Services

Business & Product Development
Annika Wallström, MSc Pharm **Product Manager**
Daniel von Sydow, MSc Pharm **Project Co-ordinator**

Customer Support Services
Anna Blomquist, BSc Pharm **Drug Dictionary Services** *(on external placement)*
Kristina Johansson, MSc Pharm **Database Services**
Anna Mattsson, BSc Pharm **Drug Dictionary Services**
Nike Meder, Pharmacist **Drug Dictionary Services**
Erica Walette, BSc Pharm **Programme Leader, Database Services** *(on study leave)*
Malin Zaar Nord, Pharmacist, **Programme Leader, Drug Dictionary Services**

Production
Johanna Eriksson **Manager**
Björn Moberg **Systems Developer**
Sven Purbe, BA **Senior Specialist**

Sales & Marketing
Mats Persson, BA **Manager, Business Development**
Hannah Ericson **Sales and Marketing Assistant**
Inger Forsell **Sales and Customer Relations Executive**
Katarina Hansson **Sales and Marketing Assistant**
Åsa Lindeberg **Web Editor, Products & Services**

the UPPSALA MONITORING CENTRE

the Uppsala Monitoring Centre
Stora Torget 3
S-753 20 Uppsala
Sweden

Telephone: +46 18 65 60 60

Fax: +46 18 65 60 80

E-mail:
(general enquiries) info@who-umc.org
(sales & marketing enquiries) info@umc-products.com
(Drug Dictionary enquires) drugdictionary@umc-products.com

Internet: www.who-umc.org

Uppsala Reports ISSN 1651-9779