WHO-UMC 24

UPPSALA REPORTS JANUARY 2004

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

Vigibase - the database story

3 million ADR reports

New Programme Member, Associates

Reports from Indian meetings

Unique classification of herbals

Data Access Rules

DIRECTOR'S MESSAGE

A very Happy New Year to you all. We ended 2003 with an excellent National Centres' Meeting in India. We were all wonderfully looked after both during the main meeting in New Delhi and in the satellite meetings in Mumbai, Agra and Mysore: thank you!

At the meeting it was clear that the activity and enthusiasm of all our collaborating partners continues to increase, with significant developments in all continents. We are delighted and proud to be asked to play a part in all of these. Moreover, the public health programmes within WHO have been increasingly keen to use our experience and support to ensure the best outcomes as they aim to treat millions of patients with scourges such as HIV/AIDS and malaria, to name but two.

the UMC funding to provide our support and services to National Centres is self earned. Our money comes from neutral tools and services, supplied to the pharmaceutical industry for their own safety purposes. Such enterprise clearly requires that we must compete and provide the best available. To this end, we are very pleased to announce our main income generator; the new Drug Dictionary, with its flexible format. We have now added a new structure for herbal products database, and, through a deal with IMS Health, will be able to offer much more extensive coverage both in the range and depth of information on medicinal products. We are also re-organising so that we can provide even better service related to our products.

The main use of the WHO Drug Dictionary is to identify and classify drugs taken for the purposes of clinical trials and recorded in spontaneous ADR reports. Data in these reports is increasingly being communicated between regulators, companies and international organisations such as EMEA and the WHO. Currently, no ICH standard exists for how such information should be documented and communicated. In order to improve the utility of the WHO-DD, the WHO proposed the discussion of our global dictionary in ICH. This is currently underway, and it would be more than useful to hear from our users (approximately 300 pharma industry users, plus all the national centres) what improvements you would like to see in the future. To re-invent the global drug dictionary will help nobody, certainly not us. To improve and develop it rationally will help everybody.

With all of our changes and improvements, the needs for our services outstrip what we can currently provide from what we can earn. For an organization whose function is to provide high quality service to both rich and poor around the world, the need also to compete commercially is challenging and needs increasing resources in itself; for example in sales and marketing.

Well, at the beginning of 2004, we are asking ourselves where do we go from here? There appear to be no independent sources of income available, and no-one, at a national or international level, who regards the work done by WHO and us as sufficiently important to partially or totally fund it.

Should the future of the body responsible for leadership in international drug safety over 30 years – with members in every part of the world – depend upon the uncertainties of trading? These are urgent issues for our WHO Programme in general.

We are working hard to find new sources of income ourselves, but we cannot do it alone, and perhaps we should not have to. I hope our friends and colleagues around the world might have some suggestions as to where we may turn.

Ralph Edwards Director *the* Uppsala Monitoring Centre

CONTENTS

5

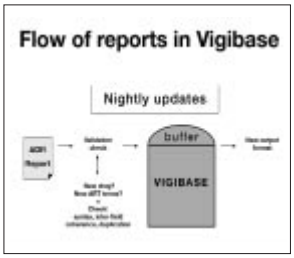
New unique classification of herbals in WHO Drug Dictionary: *the* UMC has now implemented a major revision of the nomenclature for herbal medicinal products in the WHO Drug Dictionary

6

Reports from the Annual Meeting of the WHO Programme for International Drug Monitoring in Delhi and three other Indian meetings

12

Changing the engine with the car on the road – the story of 'Vigibase', the new WHO ADR database. A massive development for *the* UMC, after 20 years of the previous version, it is E2B compatible, but can still capture reports submitted in the old INTDIS format



18

New Advisory Committee for WHO. A report of the first meeting of the new pharmacovigilance advisory committee for WHO

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UMC going on to 2007

the Uppsala Monitoring Centre has received official notification of its continued status as a WHO Collaborating Centre until May 2007. The certificate, signed by out-going Director-General Dr Gro Harlem Brundtland, redesignates *the* UMC as a WHO Collaborating Centre for International Drug Monitoring.

TEST VIGIBASE ON-LINE!

Find out more

If you want to get access to the Vigibase On-line guidelines, or if you wish to use the system live, please contact

Sten Olsson at *the* UMC (sten.olsson@who-umc.org).

It will take only a few days before you can use Vigibase On-line for managing your reports and for submitting case information to the WHO database.

Now in E2B version

In an Uppsala Reports article in January 2003 we described a new software solution for reporting and management of adverse reaction reports, suitable for national centres and others. The system, called Vigibase On-line, is based on the use of internet. Since last year Vigibase On-line has been tested further and has also been developed into a version fully compatible with the ICH-E2B specifications, which ensures compatibility with other modern adverse reaction databases. Acceptance by the EudraVigilance gateway (used by the European Medicines Evaluation Agency) has been assured. The Swiss regulatory agency, Swissmedic, has been our partner in developing the solution. Ghana has been another pilot country submitting reports to *the* UMC using Vigibase On-line.

Important features of Vigibase On-line:

- Supports seamless submission of reports from original reporter to regional centre to national centre to WHO
- Built-in error handling and validation
- Built-in multi-lingual support: already available in English, and German and French are almost complete
- Has an advanced security system that makes it available only for authorised personnel
- Designed to support parallel use by many countries
- Complete audit trail on all fields
- One server installation
- No client installation
- Less delay in reporting
- Live access to latest UMC terminologies and lexica
- Access to UMC expertise
- Integration with the search tool VigiSearch, developed by *the* UMC
- Sharing of costs and ideas

the UMC has set up an internet test site for Vigibase On-line. Anyone interested in the functionality of the system may test it on:
https://adr.who-umc.org/e2b *(note the 's')*
The test username and password is: **uruser**.

With Vigibase On-line *the* UMC offers a new level of service for national centres, taking care of a substantial part of the need for computer support. *the* UMC carries costs of licences, maintenance and service of hardware and software. Consequently there is a charge for using Vigibase On-line. The price model developed is based on the Gross Domestic Product per capita of the country. The concept is to provide a system that is affordable for everyone and cheaper than alternative custom-built software. *the* UMC has also been approached by pharmaceutical companies interested in adapting the system to their needs when reporting ADRs to authorities.

The Vigibase On-line test site – for you to try out the new reporting software.

Unique classification of herbals in WHO Drug Dictionary

the UMC has now implemented a major revision of the nomenclature for herbal medicinal substances and products in the WHO Drug Dictionary. In the new hierarchical structure all herbal ingredients of marketed products are referred back to accepted scientific botanical names. These Latin binominal names, including the Author, are confirmed through collaboration with the Royal Botanical Gardens in Kew, United Kingdom. Synonyms to the scientifically accepted names, Latin or common, are provided in a separate table. These synonyms are verified by the Department of Systematic Botany at University of Uppsala. The WHO Drug Dictionary has now become a unique source of information on accepted botanical names from all over the world.

The database structure allows the distinction between different parts of a plant and between different kinds of extracts. This is solved by the use of a Herbal Code Number (HCN) of 10 digits, employed in a similar way as CAS numbers are used as unique identifiers of chemical substances in the WHO database

Example:
The HCN 9005100502 uniquely identifies *Valeriana officinalis L.* root dry extract

Valeriana officinalis L.	90051	Plant species
Root	005	Plant part
Dry extract	02	Kind of extract

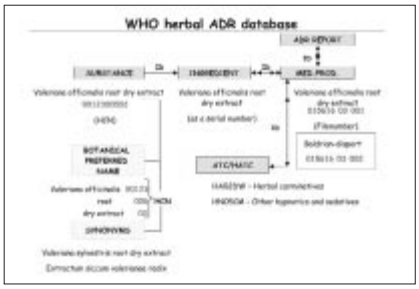
Through this solution different parts of the same accepted botanical name are regarded as different active ingredients but they may also be linked by the first five digits of the HCN. The substance register also contains information about the reference source of the name.

The table of medicinal products in WHO Drug Dictionary, which is directly linked to the adverse reactions database, contains the following:

WHO drug record number	Trade name
Source of trade name	Country
Manufacturer	Link to ingredients table
Link to ATC classification	

Herbal medicines often have many herbal ingredients which mean that a WHO drug record number can be related to many Herbal Code Numbers. The changed principles for storing information on herbal medicines affect some 1,000 herbal substances and 3,000 products in the WHO Drug Dictionary.

Herbal ATC codes are assigned to the herbal preparations in accordance with the Draft Guidelines for Herbal ATC Classification, issued by *the* UMC in 2002. The Herbal ATC provides an administrative tool for putting groups of drugs into systems according to therapeutic categories. This is useful for a number of administrative purposes and particularly for the monitoring of adverse effects of herbal drugs. The herbal ATC classification is not yet implemented in the WHO Drug Dictionary distributed to external users.



the UMC is applying its signal detection procedure to identify signals of herbal safety concerns. Getting the identification and classification of herbal medicinal products right is absolutely essential for this task. If not, signals may be generated from reports that mention a particular name e.g Aristolochia, but in fact refer to different plant species or parts with different constituents. The reverse may also happen. Signals may be missed if reports referring to the same ingredient are not brought together. The new structure allows reports referring to different kinds of extracts or different parts of the same plant to be analysed together if the assessor so wishes.

Example (*see table at bottom of this page*)
In the old structure ADR reports of products containing different preparations of Atropa belladonna were distributed on several different code numbers. In the new hierarchical structure they are kept together under one common number but still identified according to part of plant and type of extract.

Some herbal signals were analysed the past few years e.g
Ginkgo biloba L. - cerebral haemorrhage (December 2001)
Hypericum perforatum L. - unintended pregnancy (March 2002)

the UMC team responsible for the project on improved monitoring of herbal medicines are Jenny Ericsson and Helena Fucik with Mohamed Farah as scientific leader and Sten Olsson as supervisor.

Reference: H. Fucik, A. Backlund, M. Farah. Building a Computerized Herbal Substance Register for Implementation and Use in the World Health Organization International Drug Monitoring Programme. Drug Information Journal **36**, 839-854, 2002

Old substance name	**Old CAS no**	**New substance name**	**HCN**
Atropa belladonna	8001003176	Atropa belladonna L.	9008800000
Belladonna extract	0008007930	Atropa belladonna L. extract	9008800003
Belladonna herb	8500004957	Atropa belladonna L. herb	9008801000

WHO Programme meet in India

Indian government ministers address WHO delegates at the inauguration of the Delhi Annual Meeting

Workshop leaders Luisa Valdivieso, Roy Jobson, Rachida Soulaymani-Bencheikh, Abida Haq and Priya Bahri, with Bruce Hugman (Official Facilitator) taking careful notes.

Officials and guests, including Sten Olsson, nearest camera, on the dais at the Mumbai meeting

A busy and fruitful Annual Meeting took place last December as representatives of National Centres participating in the WHO International Drug Monitoring Programme met in New Delhi, India. Professor S K Gupta, Professor of Pharmacology at the All India Institute of Medicinal Sciences and Head of the Indian National Pharmacovigilance Centre welcomed delegates for the 26th Annual National Centres meeting. The meeting was inaugurated by Dr S P Agrawal, Director General of Health Services, India. Mr Ashwini Kumar, the Drug Controller General of India announced major changes to the Indian Pharmacovigilance system including the setting up of two zonal centres, 6 regional centres and 40 peripheral centres to improve the quality and quantity of reporting and the sharing of information.

Dr Mary Couper, (Quality Assurance and Safety of Medicines, WHO) gave an update from her department. She mentioned the new organizational structures within WHO with the assumption of duty of Dr Lee Jong-wook as Director-General; pharmacovigilance activities were still under the Health Technology and Pharmaceuticals cluster currently headed by Dr Vladimir Lepakhin. She highlighted:

- Growth in the WHO Programme to 72 countries, with Kyrgyzstan, Moldova, Jordan and Guatemala becoming full members
- Eight new Associate Members (Malta, Zambia, Democratic Republic of Congo, Ethiopia, Mozambique, Nigeria, Eritrea and Colombia)
- ICH meetings in Tokyo in January and Osaka in November
- Pharmacovigilance training workshop in Zambia in March (with the WHO malaria control programme)
- The 8th biennial pharmacovigilance training course organized by *the* UMC in Uppsala
- First meeting of the Advisory Committee for Safety of Medicinal Products in Geneva in October.

In *the* UMC report, Ralph Edwards mentioned that Vigibase is now fully operational and has moved from a development project to routine operations. He spoke about the 10th ICDRA meeting in Hong Kong, which recommended 'use of best methods to ensure timely reporting to WHO of case information by taking steps to increase national reporting rates' and asked member countries to consider sending reports more regularly, including daily, if at all possible. He believed developments at ICH could result in conflicting /incompatible regional/international coding systems and in the long run may jeopardize the WHO Drug Dictionary and the sustainability of the WHO Drug Monitoring Programme. Knowledge detection has improved following extension of the 'BCPNN tool kit' to identify previously unknown patterns even in the presence of missing data.

Main theme – Improving Reporting

Dr Kees van Grootheest and Ralph Edwards gave lectures on ways of improving the reporting of adverse drug reactions. The sessions underscored the universal nature of under-reporting in pharmacovigilance and suggested ways of overcoming it.

Prof Edwards questioned the basis upon which claims of under-reporting are made. When the term 'under-reporting' is used, what does it mean and what is the standard by which current reporting is compared? Is it the number of doctors per population or the number of people within a country?

Since most important ADRs occur in very rare cases there is a need for good clinical information upon which good clinical judgements and effective regulatory actions could be based. Under-reporting is not uniform; wide variations occur relating to the type of ADR and whether it is known or not, the type of medicine and the type of ADR reporting system.

ICH activities and their impact

Dr Mary Couper presented an update on ICH activities in pharmacovigilance. On E2D (Post-approval Safety Data Management), definitions and standards for expedited reporting and good case management practices have been developed. E2D is at stage IV and will soon be incorporated into ICH countries' regulations. E2E (Pharmacovigilance Planning) is intended to aid industry and regulators plan pharmacovigilance activities and provides a method for documenting risk and a structure for a pharmacovigilance plan. This is at stage II and available for wide consultation.

The WHO concept paper on the WHO Drug Dictionary was introduced at the January 2003 ICH meeting on whether there should be a single drug coding dictionary. In November in Tokyo, there was a meeting at which the concept paper was submitted for consideration by the committee. A business plan was also developed covering the different requirements in the three ICH regions, and the benefits, the effort required and cost involved in establishing such a dictionary. Regrettably, the WHO concept paper was disregarded, and the ICH proceeded to request new data elements and standards in a drug coding dictionary. While introduction of other data elements does not constitute the establishment of a new dictionary, WHO has real concerns about there being very little

time for discussion on its concept paper, the absence of any evaluation of the WHO dictionary and the complicated nature of the ICH proposals.

Drugs of Current Interest and Working Groups

15 'Drugs of Current Interest' presentations were made in theme-based sessions (epidemiological studies, CNS effects, anaphylaxis and related reactions). Working Groups focused on only one issue: Improving Reporting. Four working groups, broadly representing National Centres at similar levels of development, deliberated extensively over two days. Their work is continuing and will hopefully form the basis for a published consensus document.

2004 National Centres Meeting

Ms Niamh Arthur of the Irish Medicines Board invited participants to Dublin, Ireland for the 27th Annual Meeting to be held from 4th to 6th October 2004. This will be followed by the Annual Conference of the International Society of Pharmacovigilance from 6th to 8th October.

Mumbai, Mysore and SoPI Meetings

An international meeting with the theme: 'Pharmacovigilance - Promoting Drug Safety Through Collaboration' was held in Mumbai (Bombay) 5-6 December. It was preceded by a workshop on 'Pharmacovigilance: From Identification to Reporting' with key-note address by Professor Ranjit Roy Chaudhury and UMC contributions from Sten Olsson and Ralph Edwards. Both events were organized by the Department of Clinical Pharmacology at Seth GS Medical College and KEM Hospital with support from WHO, UMC and several Indian societies, and attracted around 200 participants.

Ralph Edwards gave the main key-note speech on 'Global Pharmacovigilance - the value of case information analysis'. Jenny Ericsson of *the* UMC presented on problems encountered with pharmacovigilance of herbal medicines and how the WHO database has been designed to deal with some of the nomenclature and classification issues. Other international contributors to the programme were David Coulter, New Zealand, Ian Boyd, Australia, Rachida Soulaymani-Bencheikh, Morocco, Robin Ferner, UK and Krisantha Weerasuriya, WHO-SEARO. The chief organizer, Nilima Kshirsagar, gave a special lecture on 'Pharmacovigilance in India: Looking to the future'.

The meetings demonstrated the great concern about drug safety issues among Indian health professionals, in both allopathic and ayurvedic medicine. There is also a growing commitment towards improving systems for recording, analysing and preventing drug related injuries. Such systems can only be achieved through collaboration between politicians, health care providers, teaching institutions, industry, media and patients.

Pharmacovigilance in South India

The Dept of Pharmacy Practice at JSS College of Pharmacy, Mysore, organised an international seminar on 'Pharmacovigilance and Medication Safety' (11-13 December). Chief organizers were Gurumurthy Parthasarathi and B.G Nagavi, and Sten Olsson gave the key-note address on 'Drug Safety Monitoring - A Global Perspective'. The international faculty included Shanthi Pal (WHO), Malcolm Partridge (UK), Tom & Adrienne Einerson (Canada), Ruth Ferguson (New Zealand), David Cosh, Stefan Kowalski and Karin Nyfort-Hansen (Australia). Sessions covered all major issues in pharmacovigilance including the theoretical basis and practical implementation of monitoring systems. Much attention was given to communicating drug safety information to professionals and patients, and how to minimise ADRs through rational use of drugs.

The hospital-based pharmacovigilance system established at JSS Medical College Hospital in Mysore, (see UR20, October 2002), serves as an inspiring model for many hospitals in India and elsewhere and many clinical pharmacists expressed interest in setting up similar systems.

Society of Pharmacovigilance, India (SoPI)

Also following the WHO meeting, the 3rd Annual Conference of SoPI took place in Agra (President Professor KC Singhal) and was well attended by international delegates, as well as younger professionals working in drug safety. The conference consisted of basic introductory sessions, plus invited and free papers, (vaccines and traditional medicines). The John Autian Oration was given by Professor Chris van Boxtel on 'Artemisia and Artemisinin – a story about toxicity'. (It is hoped to publish his presentation in a forthcoming edition of Uppsala Reports.) Professor Autian used his long experience in a perspective on 'Monitoring Adverse Effects of Medical Devices'.

An exhibition of student posters on drug safety gave an interesting insight into the ideas and views of young pharmacy students in local universities (see page 16).

Mysore Palace, rebuilt in 1912, a treasure-house of art and sculpture

Professor B J Nagavi (Principal, JSS College of Pharmacy), Bruce Hugman, Sten Olsson, and Jayesh Pandit (MPharm in Clinical Pharmacy from Mysore) at a reception

His Holiness Jagadguru, Sri Sri Shivarathri Deshikendra Maha Swamiji, the patron of JSS College of Pharmacy, and Professor Nagavi arrive for the inauguration of the Mysore meeting

Kyrgyzstan joins Programme

The latest country to become full member of the Programme is Kyrgyzstan, which fulfilled the requirements in October and is now member country number 72, with country code KG/KGZ. Head of the centre is Dr Saliya Karimbaeva from the Drug Information Centre, Kyrgyzstan.
The address is:
Drug Information Centre
Ministry of Health
3rd Linya Str 25
720044 Bishkek.

A Department of Drug Provision and Medical Equipment (DDP&ME) was founded in 1997 to strengthen and conduct state control over the market of medicinal products.

Rational use of drugs by medical institutions and population remains a major problem in Kyrgyzstan. Polypharmacy, incorrect use of effective drugs, use of ineffective drugs, irrational prescribing, all lead to increasing the number of adverse drug reactions. The problem of drug misuse is related to the lack of objective medical information among other reasons. In 1997 a Drug Information Centre (DIC) was established to address the problem of provision with evidence-based scientific information for health professionals and population.

In 1998, DIC began ADR monitoring activity and undertaking the functions of the National Center on Monitoring of Adverse Drug Reaction under DPP&ME in the Ministry of Health. Our 'Yellow card' was revised and affirmed by an order of the Ministry of Health on 25th December 2002, which obliges doctors to report all serious and unexpected ADRs. DIC is responsible for distribution, collection, primary analysis of yellow cards and relations with the WHO Uppsala Monitoring Centre. Results of ADR monitoring are published in Drug Bulletin, in this way we try to provide feedback for the ADR reports received by DIC. Another DIC Bulletin – 'Informacionnyi Vestnik' – is devoted to pharmacovigilance issues. The most actively reported health institution during a year was rewarded by the National Drug Formulary and this information was put in our Drug Bulletin.
114 yellow cards have been received by DIC since 1998. Every quarter we send the ADR reports to *the* Uppsala Monitoring Centre.

DIC shares its experience on ADR monitoring with colleagues from Central Asian Republics. Experts from National Centre of Expertise (Kazakhstan) and from Drug Information Centre (Tadjikistan) were trained on pharmacovigilance issues in Kyrgyzstan.
Today only health professionals are involved in ADR monitoring activity. This year we are going to begin our collaboration with pharmaceutical professionals and distributors of drugs through conducting short seminars.

Saliya Karymbaeva, Head of the Drug Information Centre, Kyrgyzstan writes about her centre:

National Centre staff in Bishkek, Kyrgyzstan from left to right Saliya Karymbaeva - Head Baktygul Toktobaeva - Expert Clinician Natalia An – Co-ordinator Akunbek uulu Kylychbek - Assistant

Kyrgyzstan is one of the former Soviet republics and proclaimed its independence in August 1991 (Kyrgyz – official language, Russian – official language, population approx 5,000,000, within the WHO European Region).

New Associate Members

There has been an influx of applications to become members of the WHO International Drug Monitoring Programme, mainly from Africa, but also other continents. Here is a round-up of new Associate members (those awaiting full membership status while the issue of technical compatibility of their reports with the WHO reporting requirements is being established).

Ethiopia

Halleselassie Bihon, General Manager of the Drug Administration and Control Authority of Ethiopia has contacted Sten Olsson at *the* UMC to apply for Ethiopia (population 64 million) to be accepted as an Associate. The Ethiopian agency was established in 1999, and has the responsibility for

- Ensuring safety efficacy and quality of drugs
- Promotion of rational use of drugs
- Monitoring of adverse drug reactions
- Serving as a national drug information centre

Currently the agency is engaged in promoting ADR reporting to health professionals working in all health institutions in the capital, Addis Ababa, through a video show followed by discussion about ADR monitoring. By the end of 2003 some 300 health professionals were exposed to pharmacovigilance training. As a consequence, the agency has started receiving case reports from hospitals in Addis Ababa and are expecting to see more. Abraham Geberegiorgis is responsible for policy matters and Assegid Tassew Mengistu for technical issues at the Ethiopian pharmacovigilance centre.

Malta

Dr Ray Busuttil, Director General of Health in Malta has advised Dr Lembit Rägo (Director of the Quality Assurance and Safety: Medicines section at WHO) that a National Centre for Adverse Reaction Monitoring within the Medicines Regulatory Unit (MRU) is currently being established. The National Centre on these Mediterranean islands with a population of 390,000 is to be headed by Ms Lilian Wismayer. Training and promotional activities are in progress, along with information sessions for health professionals.

Malta has entered into a formal collaboration with the Irish Medicines Board for development of pharmacovigilance in the country. Uppsala Reports plans to describe this collaboration in more detail in a future issue.

DR Congo

Dr Mary Couper has received an application from the Ministry of Health in Kinshasa, Democratic Republic of Congo, for admission as a member of the WHO Programme for International Drug Monitoring.

In a decree of 19th May 2003, Franck Biayi Kanumpepa was designated as the Focal Point for Pharmacovigilance in DR Congo, charged with putting in place a system for the detection, documentation, investigation and prevention of adverse reactions. Franck Biayi participated in the WHO/UMC training course for pharmacovigilance in Public Health Programmes conducted in Lusaka, Zambia, in early 2003. He has already received reports of serious reactions suspected of being caused by drugs used in Public Health Programmes in DR Congo.

Mozambique

We have received a beautifully written letter from the Ministry of Health, Mozambique, applying for membership in the WHO Drug Monitoring Programme. This makes Mozambique a new Associate member. We can expect them to submit their case reports soon since they keep receiving reports after having carried out training activities in two districts, Namaacha and Matutuine.

The National Centre is located at Faculty of Medicine at the Eduardo Mondlane University in Maputo and functions as a combined drug information and pharmacovigilance centre. Esperança Sevene is leader of the pharmacovigilance team. She attended *the* UMC pharmacovigilance training course in 1999 and also the Lusaka course in 2003. Esperança and her team have produced a very comprehensive plan for development of pharmacovigilance in Mozambique.

Colombia

INVIMA, the National Institute for Medicines and Food, has set up a pharmacovigilance group headed by Omar Segura. An application for membership in the WHO International Drug Monitoring Programme for Colombia was submitted in October 2003. Colombia is now an Associate with frequent contacts with *the* UMC regarding the technicalities of submitting Colombian ADR reports to the WHO database.

Nigeria

The National Agency for Food and Drug Administration and Control, NAFDAC, is establishing a national pharmacovigilance centre in the capital Abuja. Consequently NAFDAC applied for membership in the WHO Programme in November 2003. The responsible office of the Nigerian Centre is Ms Iljeoma Nnani who attended *the* UMC pharmacovigilance training course last May, as well as the recent Annual Meeting of the Programme in Delhi.

Eritrea

The Pharmaceutical Information Unit of the Department of Regulatory Services at the Eritrean Ministry of Health, Asmara, was recently designated a National Centre for pharmacovigilance. Head of the unit is Embaye Andom who underwent pharmacovigilance training at *the* UMC in 2001.

With the support of the Ministry and the WHO Regional Office he organized a pharmacovigilance workshop in October last year. Alex Dodoo from Ghana was invited as a consultant to analyse the situation in Eritrea and to participate in the workshop and other promotional activities. A Manual on Pharmacovigilance for Eritrea has been worked out and in December Eritrea were accepted as an Associate member of the Programme.

Zambia

As a direct consequence of the WHO/UMC pharmacovigilance training course in Lusaka, Zambia in March–April 2003, specifically focused on the need for safety monitoring of new anti-malarial drugs, the Ministry of Health in Zambia established a national pharmacovigilance programme and allocated a budget for its running costs. Their programme will, at least initially, be coordinated from the offices of the malaria programme.

Stop Press

As we go to press, we learn that Lithuania has also applied for membership of the WHO Programme. We welcome them as an Associate too, and hope to provide more details in the next issue of Uppsala Reports.

NEWS FROM AROUND THE WORLD

Mira Harrison-Woolrych, Director of IMMP

New Director at IMMP in New Zealand

Dr Mira Harrison-Woolrych has been appointed to succeed Dr David Coulter as Director of the Intensive Medicines Monitoring Programme (IMMP) at the University of Otago in New Zealand. The IMMP, which has a considerable international reputation, undertakes prospective, observational, cohort studies on selected new medicines. These aim to measure the incidence of adverse reactions, their characterisation, the early identification of previously unrecognised reactions and the construction of a risk profile for each medicine. The results are reported to the New Zealand Ministry of Health and to health professions. We wish Dr Harrison-Woolrych well in her new post, and send David Coulter best wishes for what will probably be a busy retirement.

Rational and safe drug use in Mongolia

The Directorate of Medical Services in Mongolia, serving a population of 2,500,000, has recently initiated a sub-council for ADRs and pharmacovigilance. This comprises a head, secretary and 8 staff from different fields of medicine.
Their responsibilities are:

- Registration of adverse reaction of drugs throughout the country
- Setting up a computer programme for management of ADR reports
- Collecting all information about ADRs and analysing spontaneous reports
- Communication both nationally and abroad
- Initiating international fellowships.

The sub-council and its staff, as yet inexperienced, are looking for support and training to assist its pharmacovigilance beginnings in Mongolia.

Mrs Nanjaa Tsogzolmaa is officer in charge of rational use of drugs in the Department of Pharmacy, Directorate of Medical Services in Mongolia. The four sub-councils working under the Human Drug Council are:

1. ADR and pharmacovigilance sub-council (as described above)
2. Pharmacology sub-council
3. Bio preparation sub-council
4. Pharmacy sub-council

The Department of Pharmacy implements the national drug policy throughout the country. It is working in close collaboration with clinical pharmacists and clinical pharmacologists, and organises joint activities through them.

In Mongolia irrational prescribing and use of medicines is a big problem. Also counterfeiting and adulteration of traditional medicines etc. is widespread. The ADR and pharmacovigilance sub-council is therefore training doctors, pharmacists as well as the general public to identify and report information to them.

UK yellow card review

An independent review of the UK Medicines and Healthcare products Regulatory Agency's (MHRA) ADR reporting system (the Yellow Card Scheme) is underway. The review is in response to an increase in requests for access to yellow card data which raise major issues in relation to public health. Looking at the access to and use of collected data, the review will be led by Dr Jeremy Metters CB, a former Deputy Chief Medical Officer.

The UK Yellow Card Scheme was set up in 1964 following the thalidomide tragedy to provide a system for early detection of emerging drug safety hazards and for the routine monitoring of all medicines in clinical use. Suspected adverse reactions to marketed medicinal products are reported to the Committee on Safety of Medicines (CSM) and MHRA, which are jointly responsible for running the scheme. Reports are mainly submitted voluntarily by GPs, hospital doctors, dentists, coroners, pharmacists and nurses. Reports are also received from the pharmaceutical industry, which has a statutory obligation to report suspected serious ADRs.

The UK's Yellow Card scheme is recognised as one of the best spontaneous reporting schemes in the world. The introduction of an On-line electronic yellow card in October 2003 modernised the way in which health professionals submit suspected reactions.

The aim is to maintain the capacity of the scheme to deliver public health benefits and prevent potential abuse of this important data in the future. It is essential to determine in what form this data should be made available.

The review's terms of reference are to:

1. identify and describe the range of issues which should be considered when considering access to data generated by the Yellow Card scheme (ethical, operational, financial and statutory)
2. identify stakeholders to the scheme and to define how such interests arise.
3. consider in what circumstances access to the data generated by the scheme could be in the public interest and the extent to which this falls within existing legal provisions
4. make proposals for guiding principles and a mechanism for handling such requests
5. make recommendations for action.

Changes at WHO Geneva

Dr Lee Jong-wook took office as the new Director General of WHO on 21 July, 2003. In that connection a series of new appointments at senior management level were announced.

It is a pleasure for Uppsala Reports to welcome back Dr Vladimir Lepakhin as Assistant Director General and head of the WHO cluster for Health Technology and Pharmaceuticals (HTP)! As was announced in UR23, he retired from the QSM (Quality Assurance and Safety : Medicines) department of WHO in April last year. He is an old friend of many working in pharmacovigilance.

Two other Assistant Director Generals have in the past taken an active interest in the WHO Drug Monitoring Programme. Dr Anarfi Asamoa-Baah, the previous head of HTP made an impressive appearance at our National Centres meeting in Amsterdam in 2002. He has now moved to the cluster for communicable diseases. The new administrative director of WHO, Dr Anders Nordström, was the head of the health department at Sida, the Swedish International Development Agency, until he joined WHO. In that position he was kept up-to-date by *the* UMC of developments in the international pharmacovigilance programme.

Merger of Spanish Agency

The Spanish Medicines Agency merged with a part of the Directorate General of Pharmacy and Healthcare Products on 30 May 2003 to form the Spanish Medicines and Healthcare Products Agency. The new Agency is now the Executive Agency of the Spanish Ministry of Health and Consumer Affairs, protecting public health and patient safety by ensuring that utilization of medicines, healthcare products and medical devices meet appropriate standards of efficacy, safety, and quality.

Address:
Agencia Española de Medicamentos y Productos Sanitarios
c/ Alcalá, 56
28071-Madrid
Spain
Telephone: +34-91-822 5018
Fax: +34-91-822 5010
E-mail: sdaem@agemed.es

Problems in Uruguay

The economic climate in South America has caused a cold wind to blow through the region's public services. Until now, the National Centres which are part of the WHO Programme have managed to keep going. However there has been very bad news from Uruguay, where all the funding from the Ministry of Public Health for the activities of the pharmacovigilance centre is being cut. The WHO has written to the Ministry in Uruguay to urge them to reconsider the loss of funding to the National Centre, particularly given the way in which the centre operates toxicovigilance and pharmacovigilance 'under one roof'. The WHO letter also points out the expertise in herbal medicine and the enthusiasm of professional staff in developing their competencies in the field.

Dr Molly Thomas – pioneer of Indian pharmacovigilance

We report with sadness that Dr Molly Thomas from the Christian Medical College & Hospital, Vellore, southern India passed away in March 2003. Dr Thomas established the Clinical Pharmacology Unit of the Department of Pharmacology, CMC, Vellore, in 1976 and was Professor and Head of the Department from 1977–98, pioneering the start of clinical pharmacology and study of adverse drug reactions. In 1983 she started the Adverse Drug Monitoring Centre in her unit. A keen pharmacovigilante, she also had a special interest in rational drug use. She served as a member of *the* UMC's signal review panel for many years. In 1999 she was elected a Fellow of the Royal College of Physicians, Edinburgh; after her retirement from Vellore she worked as Professor of Pharmacology in the Sri Ramachandra Medical College and Research Institute, Chennai. Dr Molly Thomas was associated with the WHO as a member of the WHO Expert Advisory Panel on Drug Evaluation, and the WHO Essential Drug List.

John McEwen recognised

Ian Boyd from TGA (Therapeutic Goods Administration) in Australia, reports that in June 2003, John McEwen, Principal Medical Adviser at the TGA received the Australian Public Service Medal. The citation read: 'for outstanding public service in advocating drug safety through the monitoring and reporting

John McEwen

of adverse reactions'. McEwen graduated in Pharmacy at the Victorian College of Pharmacy and undertook medical training at Royal Melbourne Hospital. From 1979 to 1989 he was Secretary of the Adverse Drug Reactions Advisory Committee and Chairman of the Advisory Board for *the* UMC. He took up his current position in 2002, having headed several sections of the TGA during the past ten years. We applaud the decision to give John a well deserved recognition for his enthusiastic work in the support of pharmacovigilance, nationally and internationally.

The redevelopment of the WHO ADR database

Creation of global database

From the start of the international movement for drug safety in the 1960s, it was recognised that pooling data in a central database in order to detect signals early was essential. The creation of an international body (the WHO Collaborating Centre for International Drug Monitoring), collecting case information in an internationally agreed format has led to a high-quality, accessible data store for use by researchers from national centres connected to the WHO Drug Monitoring Programme.

One of the qualifications for becoming a member of the WHO Programme for International Drug Monitoring is that a country must supply adverse reaction reports in technically compatible format to the WHO database at *the* UMC. Over the years, many technical modifications have been made to the ways in which data held in the WHO database were processed and retrieved. New outputs were introduced, and systems for on-line connections to the database enabling remote retrieval were developed. However, the fundamental structure, determining what kind of information could be captured and how it was stored remained unchanged from 1981 to 2003.

Impact of ICH – CIOMS

In the mid 1990s, *the* UMC decided to start work on a new database system for the management of WHO Programme case report information. The main inspiration was the CIOMS (Council for International Organizations of Medical Sciences) 1A working party on 'Harmonizing Data Fields for Electronic Transmission of Case-Report Information Internationally', - initiated by *the* UMC - who published recommendations in 1995. The focus of the new software development efforts was to implement the progress made in international harmonization. The CIOMS 1A recommendations were later incorporated into the work of the International Conference of Harmonisation (ICH) E2B working party. The goal for the new system at *the* UMC was to fulfil the needs of existing and future users in terms of internationally agreed data fields, and to improve functionality, with more efficient solutions for report handling, data retrieval and analysis.

Big change

The switch to 'Vigibase' (the new WHO ADR database) happened a year ago. This was the result of a massive development for *the* UMC, after 20 years of the previous version of the database (INTDIS). 'Vigibase' is the new database; it is E2B compatible, but can still capture reports submitted in the old INTDIS format, as well as all old data.

Hardware changes prompted the upgrading as well: we are now able to capture and handle vastly more material than when INTDIS, one of the first - if not the first - large scale relational databases worldwide, was created. The science of pharmacovigilance has also developed and is now regarded as a necessary tool to achieve safer use of medicines. The E2B recommendations have been adopted and made mandatory by regulators in the countries within the ICH - countries who are also part of the WHO International Drug Monitoring Programme. It is heart-warming that our ideas were given such credence and that all countries participating in the WHO Programme will get the advantages of using this harmonised system for information sharing which we started to develop almost 10 years ago. Major development projects undertaken within the WHO Programme are bound to be long and tedious, because of the need for proper international consultation and the lack of financial resources for major investments. In the development phase of Vigibase, further delay was caused by the bankruptcy of the major partner software company.

Updates on the road

One lesson learnt during the development phase was that, no matter how thorough the initial work to produce a user requirement specification, it was impossible to anticipate the need for further necessary specifications and modifications as the project proceeded. Re-thinking of solutions and re-programming of already completed modules had to be done throughout the project.

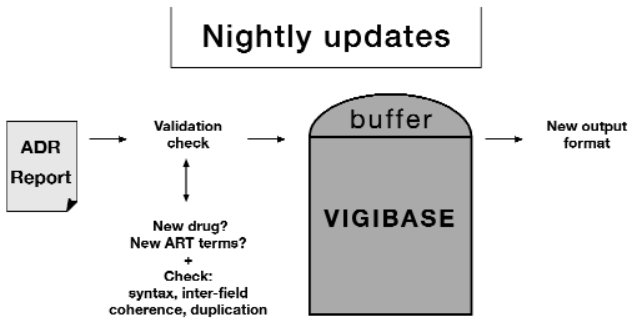
The data are stored in a relational database, which can be regarded as filing cabinets for structured information. Unlike manual filing systems, it is easy to link one set of data to another, and to sort the information by any data category. Relational database management systems (RDMS) include the data, stored in tables linked by key fields, as well as tools for data entry and retrieval. Structured Query Language (SQL) statements allow a user to define commands to the database, for instance to retrieve information from one or more tables.

Access and searchability

A new web-based database search program has been developed making use of XML (international computer language understandable in different programs). Using XML makes searching easier and also improves data handling, as data fields and their contents are kept together as part of the structured document.

Remote access to information in the WHO database takes place through internet-based interfaces, a main advantage of which is that the user does not have to install the application interface software on local computers, but can run the program from an internet browser. As new search modules are added or other improvements made, these become instantly accessible for all users, without the need for re-installation of software.

Flow of reports in Vigibase



To allow processing, ADR reports sent to *the* UMC must be in a predefined file format. In addition to 'ASCII' text files, which currently is the only accepted electronic format, Vigibase also handles data transfer using an electronic messaging format standard and a generic language for the representation of documents.

Vigibase is updated every night, so all correct reports will be entered within 24 hours of receipt by *the* UMC. Another feature is that technically incomplete reports will be stored as a searchable subset of the database in the same structure as the correct ones. The report handling system has built-in features to speed up corrections, keeping the same high quality standard. For acceptance into the ADR database, a report has to pass an extensive, error-checking procedure while in a 'buffer' data folder, involving the following:

- Syntax check
- Inter-field coherence check
- Check for duplication
- Check of drug names and adverse reaction terms.

All INTDIS reports have been converted into the new structure. By running the two databases in parallel until all quality checks were completed we have been able to receive reports without interruption during this merger. The switch to Vigibase has not affected those who wish to continue submitting reports to *the* UMC in the old format. However, it allows countries who have previously had to 'downgrade' their reports to INTDIS format for submission to resend the complete reports to capture as much information as possible (including free text) in Vigibase. The fact that the planning, development and implementation of a completely new database took place without interruption to the existing database is a major achievement unprecedented in this field.

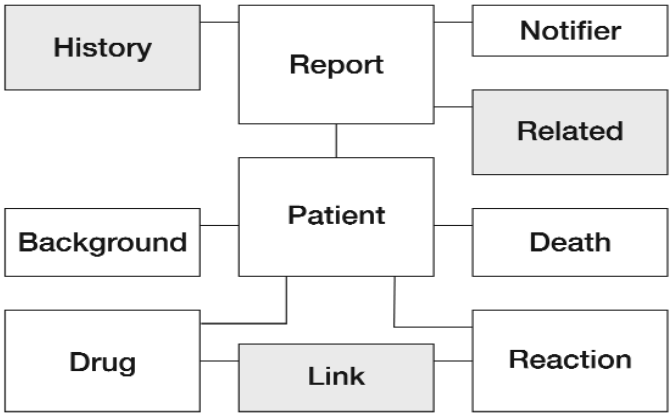
Vigibase On-line

In collaboration with Swissmedic we have developed a new web-based tool for ADR reporting for National Centres that do not have their own ADR database or do not wish to continue double entry of reports by using the INTDIS compatible WHOADR software for transfer of reports to *the* UMC. If a National Centre wishes to submit reports more than once a month, on-line reporting is worth considering – Vigibase On-line software has been developed to meet these needs.

Vigibase also includes new features of the WHO Drug Dictionary, for entering more detailed information about each drug name. The WHO ADR terminology (WHOART) is still maintained and used within the WHO Programme. However, since Vigibase is constructed to capture reports in E2B format, and ICH has declared it mandatory to use MedDRA terms, Vigibase is also compatible with these.

The WHO database, Vigibase, has these main tables

- Report: case identification, dates, classification
- Patient: identification, age, gender, outcome, causality
- Background: patient's previous illnesses/predisposing conditions
- Death: cause of death, causality, and post-mortem information



Vigibase: updated and expanded tables in white, new tables in tints.

- Related*: link to, and information on a related case
- History*: re-evaluation of a case
- Notifier: identification of the reporter
- Drug: medication, including dosage, treatment dates, indication
- Reaction: the adverse reaction, its onset date, date of resolution, seriousness
- Link*: causality assessment and information on de/re-challenge

The tables marked * are new to Vigibase.

So maybe when users are searching the new database or sending in new reports to add to it, they should spare a thought for all the effort that went into Vigibase. Perhaps it was not just 'changing the engine while the car was driving along the road', but also planning and re-designing the engine en route, which has been such an exceptional achievement.

Enquiries

If you have any enquires about the new database, the new search tool or the new reporting tool, please contact Magnus Wallberg or info@who-umc.org

4th Advanced Latin American Pharmacovigilance course

An 'Advanced Course on Pharmacovigilance' was held in Antigua, Guatemala from 24th November to 5th December 2003. Like the three previous courses (see UR20 p5), it was organised by the Spanish Medicines and Health Products Agency (AGEMED), under the leadership of Dr Francisco J de Abajo, Head of Pharmacoepidemiology and Pharmacovigilance Division of the AGEMED. As in the previous years, Dr Albert Figueras, Dr Dolores Montero and Dr Mariano Madurga also participated. The course was supported by and held at the 'Centro Iberoamericano de Formación (CIF)' of the Spanish International Co-operation Agency in Antigua. This old village was a great and beautiful setting in which to explore these topics.

Twenty-eight participants from twelve Latin-American countries spent two weeks hard at work. The course started with an overview of pharmacovigilance and risk assessment in drug regulation. Module 1 included definitions, classifications and steps to start a new national pharmacovigilance centre: all about 'risk identification'. Module 2 was about 'risk quantification'. Module 3 was on 'risk evaluation and communication'.

The course was tremendously practical with many sessions using practical cases: spontaneous reporting about counterfeit drugs, herbal medicines, vaccines and biological products; drug utilisation studies and signal generation. During the second week there were different discussions about pharmacoepidemiological cases. Different papers as epidemiological examples were discussed during the sessions.

Participants were professionals involved in regulatory affairs, in monitoring and assessing ADRs, in addition to professionals involved in pharmacovigilance activities, from academia, plus researchers and clinicians. Twenty participants came from 6 countries already members of the WHO Programme: Brazil, Costa Rica, Cuba, Guatemala, Peru and Venezuela. The rest of the participants were from Colombia, Ecuador, El Salvador, Honduras, Nicaragua, and Panama, slowly building their national systems and reporting, and aiming towards membership of the International Programme. Recently, Colombia has become an Associate Member of the WHO Programme – another very welcome development!

All participants at the course in the 'patio' of the AECI Centre in an 'Old School of the Jesus' Company', built in the 16th century in Antigua.

Curso teaching: Prof Figueras teaching to the full group.

A relaxed group preparing the discussion about practical sessions.

A group preparing a workshop with Mariano Madurga.

WHO ADR database reaches 3 million

Last November the WHO Programme for International Drug Monitoring logged the 3 millionth adverse drug reaction (ADR) report from a country contributing reports to 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* Uppsala Monitoring Centre receives over 200,000 reports from member countries each year.

Major enhancement in WHO Drug Dictionary

Health professionals in member countries report suspected problems with adverse drug reactions to their national centre (or sometimes via a regional centre), which assesses them locally and then forwards them to the WHO Collaborating Centre for International Drug Monitoring in Uppsala. Through membership of the WHO Programme one country can know if similar reports are being made elsewhere.

Using the International database

After they are processed and entered into the WHO International Database, the three million ADR reports are subject to further analysis. When several reports of a specific, new adverse reaction(s) to a particular drug are seen, this process may lead to the detection of a signal – a notice of a need for increased awareness of a possible hazard communicated to countries in the Programme. This happens after preliminary evaluation and expert review, prior to detailed work on the ground by individual national authorities.

The first ADR went into the WHO database in 1968. As groups of reports are often loaded in the database in batches, it is not certain which country was the source for number 3 million, but every report is vital to the work of the Programme wherever it comes from. The main theme of the 2003 meeting of National Centres in India was 'increasing reporting' – including presentations and working group discussions, and will lead to consensus recommendations to assist countries to boost their reporting rate. So we are already looking forward to making progress towards the next milestone!

Major enhancement in WHO drug dictionary

IMS Health collaborates with *the* Uppsala Monitoring Centre

For over 20 years, the WHO Drug Dictionary, produced by *the* Uppsala Monitoring Centre (UMC), has been the de facto international standard classification of drugs providing proprietary drug names used in different countries. Pharmaceutical companies and drug regulatory authorities worldwide use it for identifying drug names in spontaneous adverse drug reaction (ADR) reporting and clinical trials. The WHO Drug Dictionary also contains a classification system that is used for analysis and signal detection in drug safety.

Sales audit information

A preliminary agreement between *the* UMC and IMS Health, will allow enhancement of the WHO Drug Dictionary with medicinal product form and strength data. IMS is the world's leading provider of information solutions to the pharmaceutical and healthcare industries through sales audits in more than 100 countries which track pharmaceutical product sales through retail and hospital pharmacies. This collaboration will make the WHO Drug Dictionary even more comprehensive and up-to-date.

New data offers new outputs

the UMC is responsible for the collection and analysis of international drug safety data reported through national surveillance systems throughout the world. The WHO Drug Dictionary is one of the core reference tools for ensuring the coherence and reliability of data gathered in many locations and by different methods.

The collaboration over the WHO Drug Dictionary also facilitates the signal detection services the two organisations are currently providing in which they combine drug safety data and drug utilisation data. The relationship also makes a number of other services possible.

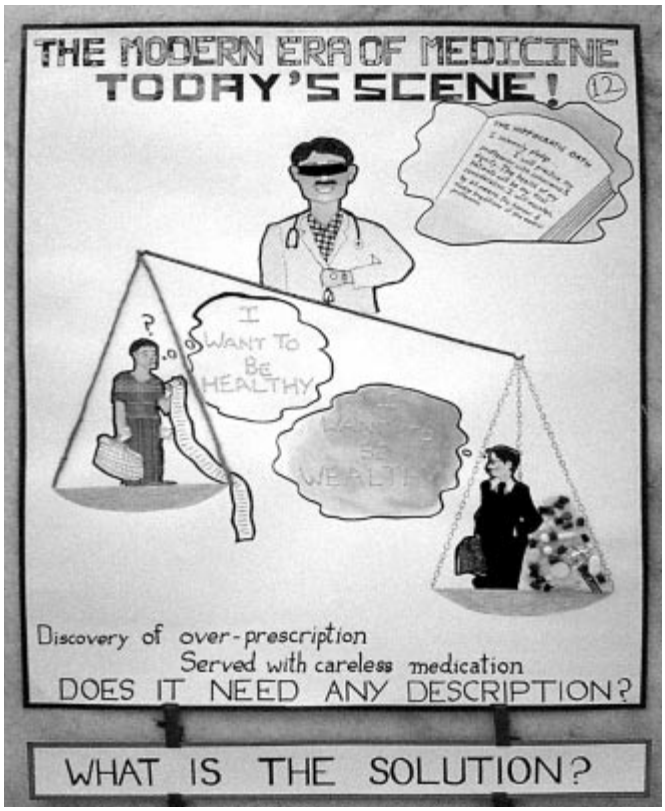
Ralph Edwards welcomed this further collaboration between the two organisations. "Based on data collection over thirty years, the WHO Drug Dictionary is already seen as a standard in its coverage of proprietary drug names. The addition of even more pharmaceutical products and the quick inclusion of newly marketed products will increase the value to public health and will greatly enhance the efficiency and accuracy of drug safety and clinical trials. I am very grateful to IMS Health for their collaboration and believe it will greatly benefit the WHO Drug Dictionary and the cause of drug safety worldwide."

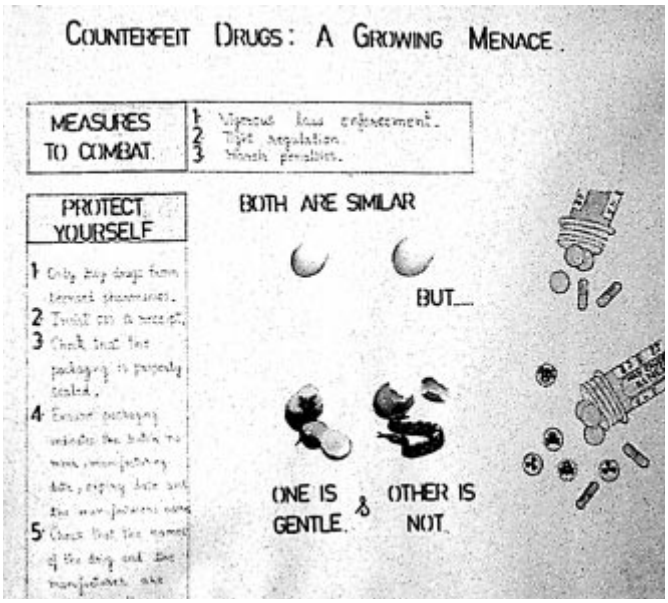
For more information, please email: drugdictionary@who-umc.org

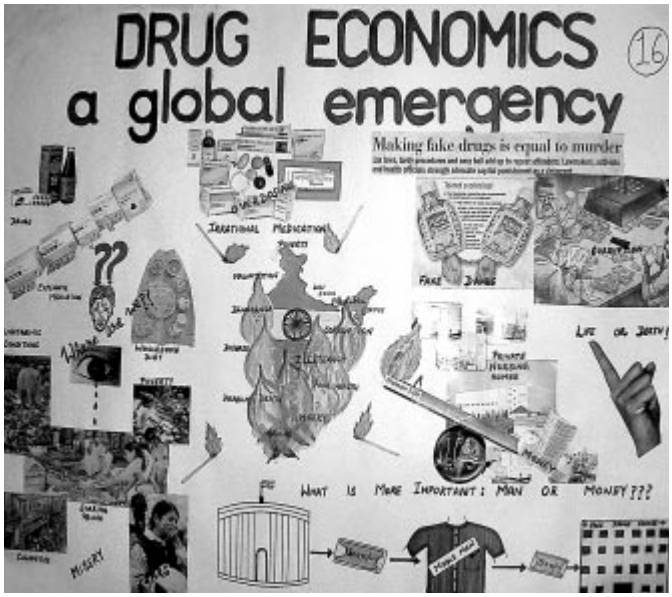
ANOTHER ANGLE ON DRUG SAFETY

During the meeting of the Society of Pharmacovigilance, India, which took place in Agra (see report on page 7), the organisers arranged a large display of posters by students from pharmacy schools in the region.

The posters displayed not only a wealth of visual materials taken from magazines and newspapers, but also artistic imagination and ability, with some striking images. There was also a good deal of idealism on the part of the young pharmacy students. Understandably many showed a keen interest in the economic and social aspects of drug safety and its place in medicine in general in India and further afield. We reproduce here a few of the interesting contributions to the display.







Professor John Autian chatting to students at the Society of Pharmacovigilance, India meeting in Agra. The students had participated in the meeting through their imaginative posters on the theme of drug safety.

Drug Safety and Poisons Centres

The value of case information analysis

Ralph Edwards raised the UMC's interest in the link between pharmacovigilance and poisoning with a presentation to the DIA last year in Chicago. Entitled 'Global pharmacovigilance -the value of case information analysis', his presentation covered the work of the WHO Programme for International Drug Monitoring and the relationship between pharmacovigilance and analysis of poisonings data.

Similar approaches?

He discussed the benefits of a similar approach being used in poison control as is used in the WHO Programme. In particular, he outlined the potential for applying the pharmacovigilance approach to chemical hazards, and how the application of data-mining technology assisted knowledge finding in large data sets.

Data-mining

The WHO Programme uses data-mining to discover new relationships in a database of 3 million reports. The data-mining or knowledge finding/discovery method (Bayesian Confidence Propagation Neural Network, BCPNN) shows disproportionality

- as new data is added;
- as data is combined; and
- in unsupervised pattern recognition.

Potential collaboration

So, given *the* UMC's role as a clearinghouse for information on drug safety, is there a role in looking at poisons data? Ralph suggested that National Drug Monitoring Centres and Poison Control Centres have complementary collaborative potential, with the former having strengths in public health, epidemiology and being close to/in regulatory affairs, while the latter can offer individual patient treatment, often acute management, and information. He argued that pharmacovigilance and poison control disciplines should move forward together. Data-mining is a major tool in both areas because of the large databases of clinical material.

Pilot study

Ralph posed another question: Is international poison case data useful? He then described a pilot example of case data analysis, where the BCPNN was used on organophosphate poisoning data collected in a multi-centre international study involving 8 countries. The IPCS (International Programme on Chemical Safety) 'Toxscore' was used to score clinical variables on 537 cases reported. The research examined the clinical variables that predict a bad outcome either singly or together, as well as considering the effect of treatment.

Grouping of treatment variables totalled 66 types, the majority (386) antidote plus gastric intestinal decontamination. IPCS Toxscore covered 33 clinical variables whilst other factors (eg weight, height, occupation code, hospitalisation) added another dimension.
The most reliable predictive single variables, in order, were:

- Coma scale
- Peripheral motor activity
- Peripheral sensory activity
- Respiratory rate
- Pa CO2

Arrhythmia predicted a bad outcome but the reverse was not true. However, the Coma scale and arrhythmia, together, indicated the worst outcome.

Use for data-mining

Data-mining is a new tool in medicine. It is very useful in preliminary analysis of complex and large databases, as it is able to identify:

- time trends;
- disproportionate data and combinations; and
- previously unknown patterns.

Using data-mining technology, analyses of large amounts of clinical data, currently NOT being used, could reveal public health trends and aid the decision making process in determining best therapy. Also, such analyses provide valuable information which is helpful in preventing illness and for educational purposes.

Ralph Edwards concluded by saying that management of ADRs and poisoning are both clinical toxicology; We should learn from the expertise of each other, and balance and use individual clinical skills and public health prevention to the best effect.

Advisory Committee on Safety of Medicinal Products holds first meeting

A newly-formed committee to advise the WHO, including its Collaborating Centre in Uppsala, held its first meeting in Geneva from 20-22 October 2003. The Advisory Committee is made up of 12 members with experience and expertise in pharmacovigilance and will provide advice to member states on issues that are important to national or international programmes and have the potential to affect them adversely if not resolved. It will advance and promote the future developments of pharmacovigilance as a discipline and will respond to identified needs of a country that may be beyond the capability of the country, and which are likely to have policy implications. It is envisaged that the Committee will meet 1 - 2 times per year. Sten Olsson and Ralph Edwards from UMC attended the current committee meeting, chaired by Dr Bruce Rowsell, Canada.

Key Programme areas

The Committee raised four key areas to promote drug safety in the WHO Programme for International Drug Monitoring:

1. Advocacy - the need to convince the public and politicians of the importance and impact of ADR reporting. A document is to be produced to outline a common vision for excellence in pharmacovigilance and the value of ADR monitoring.
2. A risk management strategy is to be put in place, and a workshop organised to develop and implement the strategy.
3. In addition to spontaneous ADR reporting, other methods such as cohort (prescription event) monitoring should be encouraged, in order to provide a fuller picture of the safety situation of particular medicines.
4. There should be additional focus in special areas such as traditional medicines.

Current concerns

The Committee also considered three specific areas, Pharmacovigilance and Public Health programmes, Pharmacovigilance for anti-retrovirals and 'current' safety issues.

Public Health Programmes could be important gateways to introduce pharmacovigilance in countries currently without safety monitoring programmes. A draft document on the idea was discussed and the Committee agreed that policy makers and public health programme managers should be target audiences. Medicines in public health programmes should be used safely and effectively to achieve best possible outcomes, and before they start, all programmes should include a medicine risk management strategy and set out to promote pharmacovigilance in the countries in which they operate. Members of the committee recognised the progress made already with the Public Health Programmes initiative on anti-malarials in Africa and recommended that the WHO as a whole should endorse this activity and it should be extended to other projects such as HIV and TB. Programmes for

The committee at work, with Dr Bruce Rowsell in the chair

elimination of lymphatic filariasis and parasitic diseases, e.g. the use of praziquantel in pregnancy, will also be reviewed.

The Committee unanimously recommended that the issue of patient safety as an aspect of the '3 by 5' initiative is of paramount importance. This initiative by WHO is aiming to provide anti-retrovirals to three million HIV infected patients by 2005.

Current drug issues that were discussed included:

- The use of a chlorproguanil/dapsone combination against malaria in an African population.
- Isotretinoin – teratogenicity
- Thalidomide (current status of registration)
- Safety considerations of traditional use of kava-kava versus modern non-water extracts

Members of the new WHO Advisory Committee on Safety of Medicinal Products line up in Geneva

A further step in opening up the WHO Adverse Reactions Database

The 10th International Conference of Drug Regulatory Authorities (ICDRA) in Hong Kong 2002 recommended that the utility of the WHO adverse reactions database be strengthened by 'opening access to the WHO database to all stakeholders with a genuine public health interest and the ability to evaluate such case information' (WHO Drug Information 16(3) 219 (2002)).

As a result of this recommendation *the* UMC will apply the following:

> **All case reports available in the WHO adverse reaction database, currently amounting to over 3 million, will be available according to the recommendation above.**

The ability to evaluate such case information will normally be interpreted as anyone with a degree level health professional education (e.g. physician, dentist, nurse, pharmacist).

Caveat Document

The case reports in the WHO database do not identify the patient or reporter. All information provided to inquirers other than the National Centres participating in the WHO International Drug Monitoring Programme, will be accompanied by a Caveat Document. The Caveat Document currently in use was adopted by the meeting of representatives of National Centres in 1989. It sets out the conditions for use and publication of data.

Until now the WHO has relied on individual National Centres to state to what extent they wish to share their submitted case reports with external inquirers . Approximately 50 countries have already agreed the rule now accepted at the ICDRA meeting. The policy given here is only a full extension of the existing practice.

Throughout the history of the WHO Programme the National Centres contributing to the WHO database have had free and unlimited access to all case information contained in the WHO database. According to a resolution passed by the World Health Assembly in 1992 (A45/13), National Centres have the freedom to use the information in the database at their discretion, in the interests of public health.

Access costs for non-Programme users

External inquirers (other than National Centres) cannot always receive case information from the WHO database from *the* UMC free of charge, however. The primary function of the Centre is to provide products and services to members of the WHO Drug Monitoring Programme. Time spent on retrieving information for other parties must be charged for. *the* UMC has developed a pricing policy to the effect that:

- Work provided which supports profit-making organisations is charged at a commercial rate.
- Work for non-profit organisations or individuals which is of a general nature (that is, in the public health, not personal interest and not a limited project), is charged at cost.
- Work of a very limited nature for a specific project will be provided free to non-commercial clients, provided that due acknowledgement is given for our contribution in any use of the work.
- More extensive work to provide free support for a client research project will be considered only on a collaborative basis, with *the* UMC staff acknowledged as co-authors on any publication and fully involved as partners in the work.

NEWS FROM STORA TORGET

New Chair of UMC Board

Carl Älfvåg on his first visit to the UMC in January 2004

UMC news

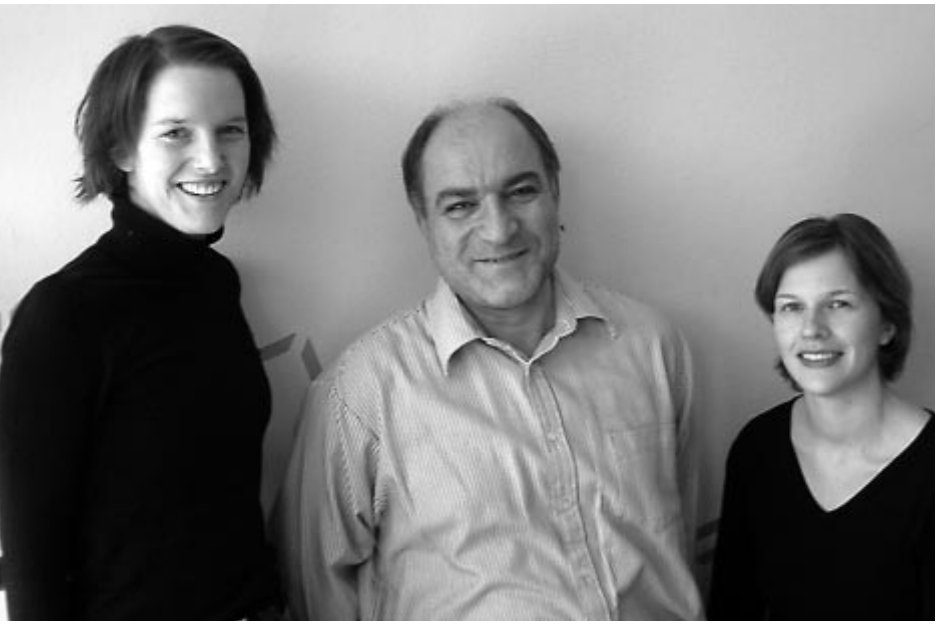
The chairman of the Board of the foundation WHO Collaborating Centre for International Drug Monitoring, Ulf Westerberg, retires after two years on his post. The Swedish Government, in consultation with WHO, has appointed Carl Älfvåg as his successor. Mr Älfvåg, is director at the Swedish Ministry of Health and Social Affairs.

Staff changes

We are delighted to introduce three new members of UMC staff who have joined us over the last year.

Anna Blomquist, working in Drug Dictionary team, grew up in Örnsköldsvik (the north-eastern coast of Sweden, and part of the 'High Coast' UNESCO world heritage area). She studied at Uppsala University, worked at various pharmacies in Kalmar, Kramfors, Örnsköldsvik, Enköping during the summer holidays and then worked for 1 year at the Academic Hospital in Uppsala, where she served partly as a ward-based clinical pharmacist. Apparently she is into thrilling activities like bungee-jump and paint-ball games.

Johanna Strandell, working in Signal Detection & Analysis, was born in Malmö in the south of Sweden and brought up in a small town in Västergötland. She entered Uppsala University in 1999, graduated in January 2001, and finished her Masters degree in science in January 2003 before joining *the* UMC. Her dare-devil activities (golf and floorball) have been curtailed since she got a dog, Dea, who takes up all her time.



Johanna, Ali and Anna

Ali Bahceci, Network Technician, is originally from Turkey and is of Kurdish origin, but has lived in Sweden since 1977. Since 1988 he has gained various IT qualifications in computer and terminals technique, networks and systems, and has experience in many types of software and operating systems. Prior to *the* UMC, Ali worked at *the* Uppsala kommun (local government); although he has lived in Uppsala for 26 years he confesses he had never heard about *the* UMC! His main escape from computers and screens is his family and children and the outdoors (fishing, the countryside).

Kiwi visitor

Dr Karyn Maclennan, a Pharmacovigilance Advisor from Medsafe in New Zealand, visited us. During her stay she met the staff, learned about our work and enjoyed the chilly autumn of Uppsala and Stockholm. It resulted in exchange of knowledge, thoughts and buying a woolen hat and gloves.

Karyn Maclennan (left) with Anne Kiuru.

New publications from *the* UMC

Assessing the Impact of Drug Safety Signals from the WHO Database Presented in SIGNAL - Results from a Questionnaire of National Pharmacovigilance Centres.
Ståhl M, Edwards IR, Bowring GP, Kiuru A and Lindquist M.
Drug Safety 2003; 26(10):721-727

Introducing Triage Logic as a New Strategy for the Detection of Signals in the WHO Drug Monitoring Database.
Ståhl M, Lindquist M, Edwards IR, Brown EG.
Pharmacoepidemiology & Drug Safety – in press.

PhD thesis news

Andrew Bate's thesis is now available at http://publications.uu.se/umu/theses/ (search on author's name 'Bate', then click on 'Fulltext' to get his thesis in pdf format)

Marie Lindquist has received many positive comments on her thesis, but not been able to thank everyone who has contacted her in person. So she would like to take the opportunity through Uppsala Reports to do so.

Both theses are available from *the* UMC – use the contacts on the back page of Uppsala Reports – there is a small administrative charge to cover postage and packing.

Doctorate for Roland Orre

Roland Orre, with whom *the* UMC works very closely on data-mining and neural networks projects, has recently received his PhD for 'Data Mining and Classification using a BCPNN' from Stockholm University.

The Netherlands

On November 17th Dr Kees van Grootheest, Director of the Netherlands Pharmacovigilance Centre Lareb, defended his PhD thesis at the University of Groningen. The title of his thesis is 'Improving pharmacovigilance and the role of the pharmacist'. The thesis discusses the place pharmacovigilance has as a scientific field, how to improve pharmacovigilance and the role of the pharmacist in the Netherlands and in other countries.

A copy can be requested via the

Netherlands Pharmacovigilance Centre Lareb,
Goudsbloemvallei 7,
5237 MH 's-Hertogenbosch,
The Netherlands.

Viewpoint

the UMC is offering a French and a Spanish translation of Viewpoint. These editions are part of *the* UMC's drive to try to disseminate information on drug safety to as wide an international audience as we can, beyond our working language, English.

Although slightly abridged, each of the new translated versions contains essential information on drug safety, benefit and risk and other big issues in health care. To receive a copy, please apply to info@who-umc.org. If you wish to receive a bulk supply for a forthcoming meeting or your professional association let us know and we will try to assist.

A text-only pdf version of Viewpoint in English is also now available to download from *the* UMC website (under 'Publications'). This should be quicker to download and print than the full version, which of course is still available by post.

Viewpoint Part 2 (scientific and technical information on the WHO Programme) will be available in spring 2004.

French & Spanish Viewpoint

WHO-ART now also available in Chinese

The WHO Adverse Reaction Terminology (WHO-ART) has previously been available in English, Portuguese, Spanish, French, German and Italian. The National Centre for ADR Monitoring in Beijing has undertaken to translate WHO-ART into Chinese (Mandarin). WHO-ART will be used for coding of ADR information within the national pharmacovigilance system in PR China. The Chinese version is available as a book, including a CD-ROM version allowing direct loading to any computer. A few copies may be obtained from *the* UMC but it can also be requested from

Center for Drug Evaluation
Division of ADR Monitoring
Building 11, Fa-Hua-Nan-Li
Chongwen District
Beijing, P.R. China
Fax: +86-10-67184951

UMC PRODUCTS & SERVICES

Split Personality

Congratulations - or should it be Llongyfarchiadau - (again) to the Swedish mail service which managed to get the following (junk) mail to *the* Uppsala Monitoring Centre. It was addressed to:

JA A Bate
WHO
Plas Gogerddan
Uppsala Monitoring Ctr
Aberystwyth SY23 3EB
S-75320 Uppsala
Sweden

Please let us know of any changes in your contact details!

Complete database of the WHO Drug Dictionary – 4th Quarter 2003

The new versions of the computerised WHO Drug Dictionary (WHO-DD) and WHO Adverse Reaction Terminology (WHO-ART), containing information for the 4th quarter of 2003 will soon be available. They will be sent to subscribers during March 2004.

Getting familiar with new DD format

This is now the forth quarter with the new C format. The CD sent to customers also contains two versions of the previous B format and all the documentation needed to make full use of the Drug Dictionary.

Need help?

If you have any queries about the content of this package, or any detail of the DD itself, or need further information about your current subscription or how to upgrade it, do call *the* UMC.

You can e-mail:

drugdictionary@who-umc.org for comments about the DD, corrections, additions, and katarina.hansson@who-umc.org for queries about your subscription.

If you are a subscriber to either WHO DD or WHO-ART and have not yet received the update, please contact Katarina Hansson (katarina.hansson@who-umc.org).

Data files for the 1st quarter of 2004 should be available during May/June 2004. The article on page 15 gives details of our latest collaboration to improve the WHO Drug Dictionary.

Exhibition presentations

UMC staff are planning to attend the following conferences in the coming months:

- DIA EuroMeeting, Expanding Horizons - Hopes and Challenges - Prague, Czech Republic, 10-12 March 2004
- 19th Annual DIA Data Management Symposium - Philadelphia, USA, 21-23 March 2004
- DIA 40th Annual Meeting - Washington DC, USA, 13-17 June 2004
- 20th International Conference on Pharmacoepidemiology & Therapeutic Risk Management - Bordeaux, France, 22-25 August 2004

We look forward to seeing many of you at these; if you wish to arrange a meeting with us, please contact Mats Persson.

What you need to know about the WHO Drug Dictionary

The Drug Dictionary is a unique international classification of drugs providing proprietary drug names used in different countries, together with all active ingredients and the chemical substances with unique reference numbers.

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

New drug names are routinely classified and added, but at a small cost it is possible to have drugs entered on request within 3 working days. Drugs are not deleted from the Dictionary, although the products may no longer be on the market.

Drugs have been entered into this database since 1968, as part of the WHO Programme for International Drug Monitoring. The database now covers drugs from all member countries of the Programme and some countries no longer existing (e.g. German Democratic Republic). Drugs recorded are those which have occurred in adverse reaction reports, but as all drugs taken by patients are included (whether they are suspected of having caused the reaction or not), the database covers most drugs used in countries in the Programme. The data are taken from official information from drug regulators, national drug compendia or other trustworthy sources. An increasing number of DD entries are entered by companies and regulators when products are launched on the market.

Future plans for the Drug Dictionary are to add more herbal and traditional medicines, though this is a huge undertaking, given the vast quantity of combinations available and the difficulties in having them appropriately classified.

In order to make our service optimal, we welcome user comments and suggestions.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
16-17 February 2004	Prepare to meet MedDRA challenges	London, UK	Pharmaceutical Training International Tel: +44 (0)20 7915 5055 Fax: +44 (0)20 7915 5056 E-mail: registration@pti-courses.com
17 February 2004	Pharmacovigilance – Compliance and Quality Assurance	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
25-26 February 2004	Monitoring Safety in Clinical Drug Development	Southampton, UK	Drug Safety Research Unit Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org www.dsru.org
10-12 March 2004	16th Annual EuroMeeting - Expanding Horizons - Hopes and Challenges	Prague, Czech Republic	Drug Information Association Tel: +42 02 61172222 Fax: +42 02 61172012
15-16 March 2004	Applied Epidemiology Training Course	Amsterdam, The Netherlands	Drug Information Association Tel: +42 02 61172222 Fax: +42 02 61172012
24-25 March 2004	Back to Basics in Pharmacovigilance	Southampton, UK	Drug Safety Research Unit Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org www.dsru.org
17-20 April 2004	2004 ISPE Mid-Year Meeting	Baltimore, Maryland, USA	International Society for Pharmacoepidemiogy Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
21-23 April 2004	Analisis y Gestion de riesgos en Farmacovigilancia	Madrid, Spain	Escuela Nacional de Sanidad E-mail: fvigilancia@agemed.es http://www.isciii.es/publico/drvisapi.dll?MIval=cw_usr_view_SHTML&tID=5644&tpr
26-28 April 2004	Le 8ème Congrès de la Société Française de Pharmacologie	Strasbourg, France	Société Française de Pharmacologie http://www.pharmacol-fr.org/
26-27 April 2004	Adverse Event Reporting and Pharmacovigilance (Introductory level)	London, UK	Pharmaceutical Training International Tel: +44 (0)20 7915 5055 Fax: +44 (0)20 7915 5056 E-mail: registration@pti-courses.com
28-29 April 2004	Adverse Event Reporting and Pharmacovigilance (Advanced level)	London, UK	Pharmaceutical Training International Tel: +44 (0)20 7915 5055 Fax: +44 (0)20 7915 5056 E-mail: registration@pti-courses.com
28-30 April 2004	International Congress of Clinical Pharmacy. How to optimize pharmacotherapy (one of the main topics is patient safety)	Paris, France	Europa Organisation - PCO Tel : + 33 5 34 45 26 45 Fax : + 33 5 34 45 26 46 e-mail: europa@europa-organisation.com www.escpweb.org
13-17 June 2004	DIA 40th Annual Meeting	Washington DC, USA	DIA Tel: +1 (215) 442 6100 Fax: +1 (215) 442 6199 www.diahome.org
1-6 August 2004	8th World Congress on Clinical Pharmacology and Therapeutics	Brisbane, Australia	CPT 2004 Congress Secretariat Tel: + (61 2) 9241 1478 Fax: + (61 2) 9251 3552 E-mail: cpt2004@icmsaust.com.au
22-25 August 2004	20th International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Bordeaux, France	International Society for Pharmacoepidemiogy Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
6-8 October 2004	ISoP Annual Scientific Meeting	Dublin, Ireland	ISoP Administration Tel/Fax: +44 (0)20 8286 1888 www.isoponline.org
12-13 November 2004	V Jornadas de Farmacovigilancia	Barcelona, Spain	Institut Catala Farmacologia Tel: +34-93 428 3029 Fax: +34-93 489 4109 E-mail: xp@icf.uab.es

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We are always happy to receive information and material for inclusion in Uppsala Reports. Short news items, or longer stories or features are both welcome. Sometimes the material we publish is taken up and re-printed elsewhere, so it can be a good way to get your news disseminated. Whether you are working in a National Centre, in academia, or the commercial sector, please send stories to Geoffrey Bowring or Sten Olsson at *the* UMC.

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