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UPPSALA REPORTS April 2007

For everyone concerned with the issues of pharmacovigilance

African Francophone training

Key pharmacovigilance papers

Vaccines and anti-malarials

News from WHO and EMEA

The Erice Manifesto

DIRECTOR'S MESSAGE

Ralph Edwards
Director
the Uppsala Monitoring Centre

We are not having an easy time getting signals, or hypotheses, published in major journals such as the Lancet and BMJ. The reasons given are that there is not enough 'proof', and (in the case of one of them) a clear statement that the format of a data mining finding, plus case series and an index case don't fit into any of their categories. Ignoring the last (but which may be a more serious reason for rejection than I think it is!), I wonder how much evidence one needs for a signal. We published the first suggestions around this matter about 15 years ago, and they are still quoted and used today, not only by us but many others (Edwards, Lindquist et al. 1990).

Since that publication in 1990, 'evidence based medicine' has come along and the industry has become increasingly aware of the need to investigate any signals that turn up on their products. Increasing media interest and the prospect of negligence litigation have made early signals that something may be wrong with a drug, which need investigating further, a 'hot issue'. All of this, I am sure, leads to reluctance to publish speculative, new signals.

I have previously commented on the value of intuition in medicine safety, perhaps the lowest level of evidence, nonetheless useful sometimes (Edwards 2004). Certainly we should never forget that some prime examples of critical signals in pharmacovigilance history are from short letters to journals, for example thalidomide and ectromelia (McBride 1961), and practolol and the muco-cutaneous syndrome (Felix 1974; Wright 1974).

How long must we continue before we accept that there is no 100% certainty and that we need to weigh all evidence, and the context in which it was obtained, against the kind of decisions we have to make, and the seriousness of their consequences to patients' health. Occasionally, single case reports will give an extremely high level of certainty, as noted in a recent paper (Aronson and Hauben 2006), and sometimes studies contain biases or are too underpowered to show anything. Evidence is infinitely variable in its strength and interpretation, as any lawyer will tell you!

In the aftermath of the thalidomide problem of the 1960s there was an emphasis on finding and publishing new suspicions about drugs so that those suspicions could be available to all, as the basis for further research and reporting. I think patients would like us to continue to behave in this way so that everybody can access the information on suspicions, as well as proven adverse reactions, if they want. The current climate does not favour this.

In this edition of Uppsala Reports I report that we have made progress in starting a pilot study on patient safety, and trying to record instances of medical practice problem signals rather than a signal of a problem with the drug itself. This will produce new speculations, this time with an emphasis on systems and people involved in prescribing, dispensing and administering drugs. It is hoped that we will do this in a 'no blame culture'.

Is it just me, or are there almost irreconcilable paradoxes in our position on improving the safety of medical practice in relation to drugs?

On the one hand, we have journals that want a high level of proof for hypotheses (signals) before publication, on the other, we have doubts about the levels of proof even in studies (despite the Cochrane Foundation's efforts) and we know studies will not be done without any hypotheses.

On one hand, we have heavy litigation over drug-induced diseases and drug scares, on the other, we have public pressures for openness and also for a no blame culture.

The trouble is that considerations of risk and benefit in medicine require balanced information and wise interpretation: very difficult, considering the above!

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More developments in the on-going improvements to the WHO Drug Dictionaries, plus improved classifications and updated ATC.

the UPPSALA MONITORING CENTRE

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

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

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

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

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Suriname joins WHO Programme

by Naomi Jessurun

Suriname is the smallest independent country in South America and is inhabited by 440,000 people. Pharmacovigilance has again been brought to our attention (two former attempts were made) after two Surinamese representatives attended the 'Training course for the Introduction of Pharmacovigilance into HIV/AIDS Programmes' (WHO/PAHO) which took place in Barbados in September 2006 (see UR35 p8).

Initiation of the centre

As ensuring safety and efficacy of all medicines on the Surinamese market is one of the pillars of Suriname's National Medicine Policy, the Ministry of Health has not only endorsed, but also welcomed the initiative of setting up a pharmacovigilance centre. After these encouraging statements a meeting with all possible stakeholders, including representatives of public health programmes, was scheduled for late October, 2006. From 1 November 2006, adverse drug reaction (ADR) reports were collected in the pharmacy of the Academic Hospital of Paramaribo (the capital), which is currently the location of the centre.

Naomi Jessurun PV coordinator with HIV/AIDS practitioners in a multidisciplinary round in the pharmacy of the Academic Hospital of Paramaribo.

Reaching out to doctors

To address and become acquainted with physicians who are most likely to report, the establishment of the pharmacovigilance centre was put on the agenda of every refresher course in the months November and December 2006. The reactions were overwhelming; physicians even reported cases from as far back as 1994. Concomitantly the co-ordinator contacted the National AIDS Programme with a view to introduce pharmacovigilance by attending multidisciplinary rounds. Since treatment of HIV/AIDS is approached through public health care in Suriname, family practitioners start and adjust treatment after consulting HIV/AIDS co-ordinators. In these rounds, which recently have been based in the pharmacy of the Academic Hospital of Paramaribo (see picture), physicians have the opportunity to present and discuss their cases. Although this is not mandatory, the meetings are usually well attended.

Link with Lareb

After a rapid start it soon became evident that knowledge concerning pharmacovigilance is lacking in this small country. As a former colony of the Netherlands, and as Dutch is still widely spoken here, Lareb (the national pharmacovigilance centre in the Netherlands) was the first centre to be asked for help. Fortunately the request was greeted with enthusiasm, and besides directions on how to assess ADR reports, their Scientific Advisory Board is willing to discuss cases from Suriname. Although there have been no formal agreements between the two centres, the co-operation is promising, especially for Suriname.

Part of the Programme

The Centre, which joined WHO International Drug Monitoring Programme in January 2007, is still immature and staffed by one person. However, this will not prevent the co-ordinator from expanding activities. In the first year the focus will be on strengthening the notification culture and implementing pharmacovigilance in the National AIDS Programme. Therefore, the first half of 2007 will be spent on implementing the reporting of ADRs as a consequence of anti-retroviral therapy within the documentation flow of patients in need of these drugs, and on stimulating reporting of ADRs by physicians working on wards in hospitals.

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Spring in Argentina

WHO Programme Annual Meeting

the UMC is delighted that for the first time the Annual Meeting of the countries participating in the WHO Programme for International Drug Monitoring are going to meet in south America. At the invitation of the Administración Nacional de Medicamentos, Alimentos y Tecnología Médica (ANMAT), the meeting will take place at the Hotel Regente in Buenos Aires from 11-13 October 2007.

The agenda

The three days will consist of plenary presentations, interactive group sessions, and the usual Problems of Current Interest sessions. Posters from country representatives are also very welcome. The opportunities for informal discussion among the international group will as ever be an essential feature of the meeting. A questionnaire has been despatched to National Centre heads and the draft programme will be circulated during April 2007.

The city

Buenos Aires is the largest city and capital of Argentina, with a population over 2.5 million located on the Río de la Plata, on the east coast of the South American continent. Heavily influenced by European culture, Buenos Aires is often called 'the Paris of the South'.

Buenos Aires is rich in culture, from museums (related to history, fine arts, modern arts), to the Teatro Colón, one of the world's great opera houses, orchestras and choirs, theatres and popular music. With its botanical garden, a large number of landscaped parks and squares and its temperate climate it is very much an outdoor city – and is teeming with football. The Nueve de Julio Avenue (named after the Argentine Independence Day, July 9, 1816), is the world's widest street. The official language of Argentina is Spanish, but most people involved in tourist activities speak some English.

Travel

Delegates will arrive at the Ministro Pistarini International Airport, called simply 'Ezeiza' which has flights from all over the world. Aeroparque Jorge Newbery airport, serves neighbouring countries and domestic traffic. The Buenos Aires Metro (known as 'el subte') is the oldest subway system in the Southern Hemisphere and in the Spanish-speaking world, currently with five lines, 80 stations, and 46 km of track.

Get ready with a guide...

A series of very helpful and practical guides in Spanish, Portuguese, Russian, French, Mandarin, German, Italian, English, Japanese and Arabic are available for download (in pdf format) from the City of Buenos Aires website. They contain useful telephone numbers, consulates and embassies, introduction to the districts, urban transport (with map) and much more;
see http://www.bue.gov.ar/informacion/?menu_id=121&tinfo=guias
(the home page is http://www.bue.gov.ar/home/).

NEWS FROM AROUND THE WORLD

Volume 9A – the revised pharmacovigilance guidelines in the EU

from Priya Bahri, PhD

Volume 9A of the Rules Governing Medicinal Products in the European Union (EU), published by the European Commission on 25 January 2007 (http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm), provides updated and comprehensive guidance on the conduct of pharmacovigilance for medicines for human use in the EU. It was drafted by the EU's pharmacovigilance experts, ie the Pharmacovigilance Working Party of the Committee for Medicinal Products for Human Use (CHMP), under the lead of the European Commission and co-ordinated by the European Medicines Agency (EMEA). The guidance is addressed to companies as well as to the authorities.

Replacing the previous human medicines-related chapters of Volume 9, which compiled the EU pharmacovigilance guidelines for the first time in 2001, Volume 9A implements the revised pharmaceutical legislation, ie Directive 2001/83/EC as amended in 2004[1] and Regulation (EC) No 726/2004[2]. It also takes into account recent EU legislation on clinical trials and medicines for children. New concepts are the description of the company's pharmacovigilance system and, if needed, the product-specific risk management plan, to be submitted with the application for marketing authorisation. This is complemented by pharmacovigilance inspections which may now be conducted at random or in response to concerns over non-compliance. The use of established spontaneous reporting systems also for cases of suspected transmission of infectious agents via a medicinal product is another important new element. Furthermore, electronic transmission has become mandatory for single case reporting. The procedures for the authorities have been updated too, with view to increased harmonisation and work-sharing. This includes the guidance on collaborating with WHO[3]. A new chapter on direct healthcare professional communications, commonly known as "Dear Doctor-letters", is a start for improved communication to the public.

Volume 9A was subject to public consultation and continues to be a platform for dialogue between stakeholders on good practices for the conduct of pharmacovigilance. Therefore, it will stay a living document, being updated and complemented in the future.

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Sweden endorses patient reporting

In December 2006 the Swedish Medical Products Agency presented (in a report to its government) further measures for improving pharmacovigilance in Sweden. One of the proposals was to initiate general consumer reporting within Sweden. This proposal was preceded by a pilot project with consumer reporting in the Uppsala region. A form specifically developed for reporting by consumers was available at Uppsala community pharmacies and help from staff was given on request. This exploratory study demonstrated a high compliance of responding to the most essential requested information and indicated that consumer reports may be an additional source of information of ADRs. This extension of reporting is expected to contribute with reports about ADRs to over-the-counter products and herbals, and to give further information on ADRs causing compliance problems. In the interim analyses the consumers did not strongly prefer any mode of reporting whether through healthcare professionals, pharmacies, forms on paper or internet or by telephone calls.

Läkemedelsverket, the Swedish Medical Products Agency

Based on the population size and the reporting ratio by consumers within this region, numbers indicate that as many as 5,000 to 7,000 reports could be expected annually when implemented nationwide. The Swedish MPA is presently preparing the final technical solutions for reporting and investigating the forms for feedback of information to relevant parties - including the consumers.

Vaccine Safety

Global Advisory Committee on Vaccine Safety

from Adwoa Bentsi-Enchill

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body, was established by WHO to deal with vaccine safety issues of potential global importance independently from WHO and with scientific rigour[1]. GACVS held its 15th meeting in Geneva on 29–30 November 2006. The committee discussed a number of general issues relevant to all vaccines as well as a number of vaccine-specific issues; a full report of the meeting has been published in the *WHO Weekly Epidemiological Record*[2].

Monitoring vaccine safety

At previous meetings[3,4] the GACVS requested that global vaccine pharmacovigilance be strengthened, particularly within the WHO Programme for International Drug Monitoring. Aspects needing attention include data transmission by countries, data quality assurance, and the processing and analysis of data, including timely signal detection and action. As a result, a sub-group of 6 GACVS members was formed to work with the secretariat to ensure that the initiative continues to move forward[4]. A report of the sub-group's activities was presented to the full committee. The specific terms of reference of this sub-group are: to advise WHO on the development of a high-quality system for reporting, detecting, analysing and communicating adverse events following immunization (AEFI) at a global level; and to advise WHO, the WHO Collaborating Centre for International Drug Monitoring (*the* UMC) and Member States on specific issues relating to activities aimed at achieving the first goal. Specific objectives have been agreed, and the sub-group will undertake these over the next couple of years. A high priority is to raise the profile and awareness of pharmaco-vigilance within the immunization community using existing WHO networks and other means.

A report on a visit to *the* UMC by the secretariat and sub-group was presented. Key areas for action include:

i) increasing vaccine-specific expertise at *the* UMC through creation of a position dedicated to vaccine safety
ii) assisting in recruitment of additional expert signal reviewers; and
iii) engaging scientific experts to consider what methods are best for detecting vaccine safety signals.

Deficiencies with respect to vaccines in the anatomical therapeutic chemical and defined daily dose (ATC/DDD) classification and WHO's Drug Dictionary need to be addressed. A programme of work is planned to propose modifications to the ATC/DDD to be presented to the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway.

Vaccine formulations

At the last GACVS meeting, the committee recommended to look into the real and perceived safety of preservatives and other inactive ingredients in vaccine formulations. The limited information provided about excipients, in contrast to the active components, in vaccines was highlighted. This is a challenge for drug regulators and industry in the areas of quality assurance, and for health professionals in terms of communicating risks. The infrequent administration of vaccines makes it unlikely that small amounts of excipients are toxic. However, this may change with the development of therapeutic vaccines, which might be administered repeatedly. A mechanism must be established to secure more information about detailed vaccine formulations and to rigorously review the safety of excipients. A GACVS sub-group was established to examine this issue further and will report on its work at the June 2007 meeting.

GACVS web pages

Pandemic influenza vaccines

The committee discussed plans for the global monitoring of the safety of pandemic influenza vaccines. Developing a robust network of contact points to share information and pilot the system during seasonal influenza immunization is vital to ensure that Member States have rapid and timely access to safety information, to provide access to dedicated resources able to address urgent queries, and to initiate and co-ordinate responses. A web-based platform to support the collection and dissemination of information to relevant stakeholders is being developed.

The availability of several global surveillance systems for communicable diseases, drugs or vaccines may be relevant to monitoring pandemic influenza vaccines. The global post-marketing surveillance network aims to co-ordinate resources and supplement areas not sufficiently addressed. A sub-group of GACVS will be formed to pursue this goal in connection with WHO regulatory preparedness workshops on human vaccines for pandemic influenza.

How the committee works

In addition to regular reports in the *Weekly Epidemiological Record,* the scope of the committee's work has been published[5]. The committee's recommendations and conclusions, together with additional information on topics discussed, and its terms of reference are posted in the six official UN languages on the GACVS web site at http://www.who.int/vaccine_safety/en/.

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ACT follow-up in sub-Saharan Africa

by Dr Mary Couper

Intensive follow-up course in pharmacovigilance for African countries introducing artemisinin-based combination therapies (ACTs)

In 2003 a first training course was organized in Zambia to introduce pharmacovigilance for malaria programmes into five countries in sub-Saharan Africa, namely Burundi, Democratic Republic of Congo, Mozambique, Zambia and Zanzibar (see UR22, p5).

The 2007 course in Zambia, on 5-7 February was a follow-up with the objectives of reviewing progress made in these countries in implementing their action plans for pharmacovigilance, providing advice on database management and providing more detailed information on how to conduct active surveillance studies for pharmacovigilance for African countries introducing ACTs.

The facilitators were David Coulter (New Zealand), Alex Dodoo (Ghana) and Magnus Wallberg (UMC). The secretariat from WHO consisted of Loyce Lishimpi and Fred Masaninga (Zambia), Issa Sanou (Brazzaville), Walter Kazadil (Gabon), Monica Olewe (Zimbabwe), with Andrea Bosman and Mary Couper from WHO-HQ in Geneva. Funding provided by the European Commission to strengthen pharmacovigilance in African, Caribbean and Pacific

David Coulter and Henry Irunde (Tanzania) in discussion

States ('ACP') countries helped make the course possible.

The programme aimed to achieve:

1. A simplification of the WHO draft protocol (March 2003) for spontaneous reporting of adverse events following treatment with artemisinin-based combination therapy
2. Understanding of the requirements of a pharmacovigilance database: potential adoption of *the* UMC's case management system VigiFlow (formerly Vigibase Online)
3. A core protocol for cohort event monitoring to complement spontaneous reporting systems that could be used as a template for other countries
4. Country plans for strengthening pharmacovigilance of ACTs.

The first day was spent introducing the subject and providing an update on VigiFlow. Magnus Wallberg gave a comprehensive

Dr Stella Anyangwe (WHO Representative in Zambia) at the opening of the Lusaka meeting, with Dr Mary Couper on her left

presentation and a practical demonstration of its value. VigiFlow is a useful tool in the management of data, but dependent upon a good internet connection. The second day consisted of presentations on active and passive surveillance systems by Alex Dodoo – the value of each was discussed in detail. David Coulter then gave detailed presentations on the different aspects of cohort event monitoring. The third day was spent on reviewing the progress, developing recommendations, presenting country action plans for pharmacovigilance and establishing the needs for a simplified protocol.

The course made the following recommendations:

- Countries to prioritize and strengthen pharmacovigilance activities
- Countries to advocate pharmacovigilance at regional level through regional economic bodies
- Countries to integrate national ADR forms and guidelines for spontaneous reporting in malaria case management training manuals and guidelines
- Countries to introduce cohort event monitoring in the way most appropriate to the local situation, to complement spontaneous reporting and pick up potential signals from use of new drugs including ACTs
- WHO to provide technical and financial support to countries in the implementation of the pharmacovigilance plan of action
- WHO to negotiate free access to VigiFlow and develop a similar method for cohort event monitoring for countries to strengthen the national pharmacovigilance systems.

Based on the materials of the course, a manual providing guidance for pharmacovigilance as an integral part of malaria programmes will be developed and further training courses will be organized using this material. Expert consultants will provide technical support and in-country training with regular communication and follow-up after the country visit.

Training in database management (eg VigiFlow, Vigibase, VigiSearch) will be carried out. VigiMAL (an international e-mail network of interested professionals, academic institutions, *the* UMC and WHO) will be reinvigorated.

Francophone Pharmacovigilance Training

Shanthi Pal reports

'When a road is good, it will be used a second time'

Thirteen countries* from Francophone Africa came together for a two-week pharmacovigilance training course in Rabat, Morocco from 12-23 February 2007. The course was conducted in French and organized by the national pharmacovigilance centre in Morocco with the support of WHO, the United States Pharmacopeia Drug Quality and Information Program (USP DQI), USAID and the Ministry of Health of Morocco.

The training had an 'earth-shaking start', literally, with a brief seismic shock running through Rabat on the very first day of the course. The programme covered all aspects of general pharmacovigilance, touched upon specific issues in monitoring the safety of medicines in HIV/AIDS and malaria and introduced participants to complexities such as establishing a temporal relationship between the cause and the effect. The usual hands-on training with databases and tools for collecting spontaneous reports of adverse reactions were included too, with several group exercises making the whole process very interactive and useful for the participants.

Teachers and participants at the course in Rabat.

For various reasons Africa, particularly Francophone Africa, has remained more or less outside the pharmacovigilance zone of influence. At present 18 African countries participate in the WHO Programme for International Drug Monitoring (nine full members and nine Associates). Very few of these belong to the Francophone regions. In that sense, this course was long overdue, and hopefully, is only the first of many more to come. These initial efforts need to be sustained for pharmacovigilance to become a reality in Africa as a whole.

Despite all its hardships, Africa stands for compassion and colour, warmth and enthusiasm, good humour and relentless optimism. The participants brought all of these to the course, and in turn were treated to the technical competence, the spectacular hospitality and good-will of the staff of the Moroccan Centre. Managed by its nearly all-women team, the Moroccan Centre is clearly a facility of excellence. According to an African saying 'When a road is good, it will be used a second time'. The Moroccan Centre will no doubt be approached again, by other countries wishing to implement pharmacovigilance in their national programmes.

***The participating countries were:** Algeria, Benin, Burkina Faso, Cameroon, Cote D'Ivoire, DR Congo, Gabon, Mali, Madagascar, Sao, Tome et Principe, Senegal, Togo, Tunisia

Pharmacovigilance training – a multifaceted challenge

Sten Olsson comments

The recent training course in Morocco described by Shanthi Pal is a landmark event in the history of pharmacovigilance training. *the* UMC has carried out ten courses for an international audience since 1993. More than 230 professionals from 92 countries have attended these 2-week courses. This training activity has lead to a rapid expansion of the WHO pharmacovigilance programme. However, all UMC courses have been in English; areas of the world where English is not widely understood have been disadvantaged. The Spanish Medicines Agency took the initiative of running pharmacovigilance courses for Spanish-speaking Latin America from 2000-03, and similar international courses have been carried out in Spanish by agencies in Argentina, Chile and Venezuela. *the* UMC spoken at some of these aided by interpreters. Similarly *the* UMC has contributed to pharmacovigilance courses for Russian-speaking audiences and for two Chinese-speaking delegations in Uppsala.

We hope that the Moroccan centre's adaptation of the 2-week UMC training programme to an African French-speaking audience will result in the countries involved being stimulated to actively join the WHO Programme. *the* UMC does not have the resources to overcome all the existing language barriers. We would encourage other national centres to emulate the Moroccan centre, and provide basic pharmacovigilance training in languages other than English.

the UMC received a record number of applicants for its 11th international course in May 2007: 87 candidates from 49 countries in five continents competing for the 25 places available. Even if only one candidate per country is admitted to *the* UMC course 24 countries miss the opportunity of having a professional receiving basic training in pharmacovigilance methodology – a most unsatisfying situation.

In summary there is an urgent need for

- training in pharmacovigilance methodology to be offered by competent organizations
- additional sources of funding, for course organizers and participants
- pharmacovigilance training in many different languages.

the UMC is discussing with the International Society of Pharmacovigilance (ISoP) and other partners to increase the global capacity for pharmacovigilance training.

ACSoMP meets again

The WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) met in Geneva 26 – 27 February, 2007. The Committee is composed of 12 members drawn from the WHO Expert Committee for Drug Evaluation and for Drug Policies and Management and from other expert advisory panels. Staff from the QSM unit (Quality and Safety: Medicines) at WHO and *the* UMC provide the secretariat of the Committee. It has met every year since 2001 to advise the WHO Programme for International Drug Monitoring and member states of WHO on safety issues relating to medicinal products.

Wide role

The Committee responds to national regulatory authorities and to national programmes, notably public health programmes, on highly technical or scientific issues where implications are controversial, and on policy and research issues where these may be problematic. The Advisory Committee in its work also serves to further the principles and scope of pharmacoepidemiology, to promote communication in this field, and to encourage training and capacity building in countries where there is little activity in the field of pharmacovigilance.

Achievements to date

The Committee has had several concrete outputs over the years. Guidelines have been produced and endorsed. The Committee works continuously towards the introduction and implementation of the safety monitoring of medicines in all WHO Public Health Programmes. This has resulted in an active collaboration with several programmes including immunization, malaria, HIV/AIDS and programmes for de-worming and elimination of lymphatic filariasis. Another key activity has been to provide input to the World Alliance on Patient Safety. The ACSoMP has been consulted over controversial issues like chlorproguanil/dapsone and Kava.

Children and essential medicines

At the February meeting the Committee reviewed a manuscript on the safety of medicines in children. Once published this will be an important addition to the series of publications on safety monitoring. The Committee also, for the first time, evaluated data on the toxicity of medicines that have been submitted for addition to the WHO Model List of Essential Medicines. The contribution from the Committee will add substantial value to the process of updating this list. ACSoMP also discussed the development of a uniform research methodology that may be used around the world to study the burden of medicine-related morbidity.

A surprise guest

An unscheduled, and very popular, event at this particular ACSoMP meeting was the visit of the new WHO Director General, Dr Margaret Chan, at the cocktail that ended the first meeting day. Instead of making instant commitments of her support for the work of the Committee she invited a written briefing note about the work of the Committee and the challenges facing it, which of course she was provided with shortly afterwards.

Mary Couper, Lembit Rägo, John Haines (INTOX),, Kenneth Hartigan Go, Margaret Chan, Shanthi Pal, Nilima Kshirsagar, Rachida Soulaymani-Bencheikh

Present ACSoMP members

Ms Niamh Arthur, Ireland
Dr Jürgen Beckmann, Germany
Dr David Coulter, New Zealand
Dr Gerald Dal Pan, USA
Mr Murilo Freitas Dias, Brazil
Dr Kenneth Hartigan-Go, The Philippines
Mr Li Dakui, PR China
Dr Nilima Kshirsagar, India
Dr Vladimir Lepakhin, Russia
Dr June Raine, United Kingdom (chair)
Dr Gunilla Sjölin-Forsberg, Sweden
Dr Rachida Soulaymani-Bencheikh, Morocco

The Erice Manifesto 2007

Drive for new vision in pharmacovigilance

Bruce Hugman reports

From time to time all human activities need review and new focus and energy. The Erice Manifesto, recently launched in Drug Safety[1], arose from a review of the current state of worldwide pharmacovigilance and presents a powerful vision of how the science might adapt and grow to meet the needs of the new century.

The Manifesto offers five main areas of challenge, described in the following terms:

- Placing the welfare, safety and concerns of patients at the absolute centre of all thinking, planning and operations, and measuring the value of all activities against those non-negotiable priorities
- Transforming medicines regulation from a centralised, sometimes distanced, bureaucratic operation
- Adopting innovative, proactive approaches (including emergent science such as pharmacogenetics and personal informatics) and learning from other social and industrial sectors (such as aviation) where safety is a core aspect of operations
- Pursuing open, altruistic collaboration at all levels and between all parties worldwide
- Ensuring that activities are based on all available, evaluated, transparent evidence and include powerful tools for feedback, impact assessment and review, for shared, global use.

Under each of these there are detailed, specific proposals for the development of effective, modern practice, some of them radical in their intent and implications.

Sicilian think-tank

The group behind the Manifesto, like that responsible for the Erice Declaration of 1997, has no formal constitution or representative credentials. Both were brought together informally at the Ettore Majorana Centre in Erice, Sicily, under the aegis of the International School of Pharmacology, with Professor Giampaolo Velo and *the* Uppsala Monitoring Centre facilitating the meetings. The Manifesto group was the smaller of the two, involving twenty-seven experts from twelve developed and developing countries.

Like all consensus documents, the Erice Manifesto represents views acceptable to the whole group; its proposals, therefore, do go somewhat further than some might have wished, and stop short where others may have felt more forthright recommendations should have been made. However, the dense and detailed text provides the basis for a radical reappraisal of pharmacovigilance on the basis of which countries and organisations can take reform as far as they wish. Most items on this detailed agenda call for a conference in their own right.

Reform

The Manifesto's subtitle, 'For reform of the safety of medicines in patient care', clearly declares the depth of the challenge: while pharmacovigilance has delivered great benefits, the time has come for a reconceptualisation of its core purposes and activities, the breadth and priorities of its concerns, and the spirit of patient-focused collaboration in which it is conducted.

The group was especially concerned that drug safety, in all its aspects, remains undervalued and under-resourced, and still something of a mystery to patients and the public: their hope was that the Erice Manifesto would bring these issues to high profile public, political and media attention, and provoke worldwide debate and progress.

1 The Erice Manifesto: For Global Reform of the Safety of Medicines in Patient Care. Drug safety, 2007; 30(3): 1. A copy of the Erice Manifesto accompanies this edition of Uppsala Reports.

My Top Five Papers

Dr Božidar Vrhovac, MD, PhD, FRCP, Professor Emeritus, University of Zagreb; Croatian Academy of Sciences and Arts, Corresp. Member, Zagreb, Croatia

Božidar Vrhovac

Božidar Vrhovac graduated in medicine in 1961 at the Medical School University of Zagreb, at that time in Yugoslavia, now in Croatia. After obtaining clinical experience

in the Emergency service of Zagreb he started his university career followed by specialization in internal medicine, where he spent a year at University College, London. This lead to the development of clinical pharmacology in his country through the Division of Clinical Pharmacology (the first in former Yugoslavia) within the Department of Medicine in the University hospital. In 1974 Yugoslavia joined the WHO monitoring programme as the 18th country. For over 30 years the operational base of the National Centre (until the recently-formed Medical Agency was founded), was this Clinical Pharmacology section led by Božidar Vrhovac.

He devoted his career to the rational use of drugs and knowledge of ADRs; as a part of it editing a number of books (IV. edition of the Internal Medicine Handbook is in preparation) and Formularies. In 2004 he became a Fellow of the Royal College of Physicians, London. Vrhovac's publications range from national (ethics, health, clinical trials, health protection) to international editions (Meyler's Side Effects, Clinical Pharmacology - McGraw Hill). He has held posts on various CIOMS and WHO working groups. As Emeritus Professor of the Zagreb University he continues to be active in teaching and education at undergraduate and postgraduate levels.

Developing ADR monitoring in a small country 30 years ago was a difficult task. At the beginning of reporting and analyzing ADRs in Yugoslavia, publications not scientific in the real meaning of this word should be mentioned:
WHO Technical Report No 446 (1970) Clinical Pharmacology, Scope Organization and Training, only mentions 'drug toxicity and therapeutic disasters' once. *No 498* of the same series, *(1972) International Drug Monitoring, The Role of National Centres* was of great importance for all countries and individuals who needed arguments to convince the health authorities that ADR monitoring and national ADR centres are necessary.

Of major importance in the beginning of ADR monitoring were meetings organized from 1972 with financial support of the German government entitled 'The role of clinical pharmacological evaluation in drug control'. The 5th meeting in 1976 had a number of presentations dealing with ADRs. At the 6th meeting discussions were held on the importance of post-marketing surveillance giving, naturally, importance to the ADR monitoring.

These publications gave a strong impetus to the ADR monitoring activity in countries like Yugoslavia due to the considerable authority and importance – possibly more than today – of WHO for less developed countries. While countries like the UK and Sweden already had a monitoring system (UK in the period 1964-1970 collected 24,000 reports, 54% from GPs) in countries like Yugoslavia the importance of this aspect of pharmacotherapy was almost unknown. At the start of ADR monitoring, manufacturers took any mention that their products could also have unwanted effects as an offence, and physicians ignored this possibility considerably.

Bearing in mind the characteristics of ADR monitoring in Yugoslavia when the programme started (and later in independent Croatia), I have chosen the following articles listed in date order according to their impact on me, my co-workers and our work at the time they were published:

Klimt CR, Knatterud GL, Meinert CL, Prout TE (UGDP). A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. *Diabetes,* 1970; 19:747-830.
This was for me the first big randomized study giving unexpected results contrary to the prevailing opinion at that time, about usefulness of hypo-glycaemic drugs. In spite of many weaknesses (concentration of deaths in some health centres, often low comparability of patients groups etc) the study was important for Yugoslavia since in our opinion there was a realistic possibility to repeat such a study in Yugoslavia (Zagreb had and still has a strong Diabetic 'Vuk Vrhovac' institution). This plan failed since the Yugoslav government did not or could not meet the costs.

Karch FE, Lasagna L. Adverse reactions. A critical review. *JAMA*, 1975; 234:1236-41.
As mentioned in the previous edition of *Uppsala Reports*, this paper is still used today when pharmacovigilance is being discussed, and used in teaching and education, including by me. It explains the difference between 'events' and adverse reactions, trying to define various probabilities of the causative relationship between ADR and the probable causative agent.

Years after the paper appeared, I asked Lou Lasagna how he explained this enormous international interest aroused by his article and had he expected such a response. He modestly answered "probably they found it useful".

***Fattinger Karin, Roos M, Vergeres P et al. Epidemiology of drug exposure and adverse drug reactions in two Swiss Departments of internal medicine. Br. J Clin Pharmacol.*, 2000; 49:158-167.**
The main reason I have chosen this description of an event monitoring system is that its results could be compared with observations obtained in our Croatian clinic. The analysis of 4,331 hospitalizations which took place in this highly developed country during the period of 8 days showed that in 50% of all hospital days the patients were exposed to between 4 and 9 different drugs. In at least 41%, one disease unrelated event could be possibly attributed to pharmacotherapy. Clinically relevant ADRs occurred in 11% of all hospitalizations. ADR-related deaths were suspected in 1.4%. In a similar study in our clinic, 4% of hospitalizations were caused by ADRs but the number of drugs given to patients was higher than in Fattinger et al.

It is important to stress that such studies can be extrapolated only with difficulty to other hospitals and countries. They should be repeated as often as possible not only to get one's own data but also to raise interest of health professionals, not only physicians and students, for unwanted effects of drugs.

***Writing Group for the Women's Health Initiative Investigators. Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women.* JAMA, 2002; 288:321-33.**
I choose this randomized primary prevention study of oestrogen and progestin component for several reasons. The most important are: firstly the considerable number of women (16,608) who have been followed for more than 5 years; secondly the results were unexpected and contrary to the accumulated observational evidence, indicating usefulness only for colorectal cancer and hip fracture, showing an absolute excess risk of events of 19 per 10,000 person-years. The trials stimulated by the WHI study confirmed the WHI results in various forms.

The WHI trial was an important piece of knowledge about HRT, which was very intensively advertised especially in developed countries.

***Pedersen TR, Faergeman O, Katelein JJP et al. High-Dose Atorvastatin vs Usual-Dose Simvastatin for Secondary Prevention After Myocardial Infarction, The IDEAL Study: A Randomized Controlled trial.* JAMA, 2005; 294:2437-45.**
This secondary prevention study improved our knowledge about, at this time, a very important therapeutic group. The effectiveness of statins is well proven but the relative characteristics of various statins much less. The IDEAL trial indicated that a small dose of one statin, usually the cheapest (simvastatin), has practically the same effect as a high dose of a widely-advertised other member of this group (atorvastatin). Contrary to the advertisements there was no difference between the mentioned statins in cardiovascular and all cause-mortality. The higher dose caused, as expected, more drug discontinuation due to non-serious adverse events.

Statins are now widely prescribed, although many claim not sufficiently. If accepted, these results will have an economic component, helping health services to use resources for better proven activities.

Patient Safety Project

Following discussions over the last year, an agreement has been reached for an international one year pilot patient safety project funded by the WHO Global Alliance on Patient Safety. The essentials of this new project are given below.

National centres

In order to obtain more information on medication errors, the volunteer national centres with the WHO Programme for International Drug Monitoring should conduct activities as follows:

- Collect and identify reports with significant medication errors
- Establish consensus of the kind of reports which comprise the most significant situations for medical practice (eg from poison control centres, hospitals), and the reporting formats which are most useful
- Begin to operate root-cause, or other agreed, in-depth analysis of comprehensive causes
- Analyse the collated information for new signals, especially for those which may have a systematic cause in medical practice
  - to identify situations, occurrences, incidences, etc. that are most prone to errors and establish preventive programmes, eg intensive care units.

The analysis of data will need terminology and data mining methods adapted to the new concept of patient safety, in order to detect signals and therefore put into place preventive strategies. As is the case for ADRs, medication errors will be submitted to *the* UMC by methods commonly used by the different countries.

The countries will try to co-ordinate their experiences as they go along. There is much variation in the societal and professional settings of the national centres and the pooled knowledge is likely to be rich and varied. The co-ordination will be carried out by the National Centre in Morocco, which has already conducted significant work in this area.

the UMC

the UMC will do the following to ensure the key success factors for the project are achieved:

- Institute an agreed way of identifying 'patient safety reports' prospectively
- Work on areas which are likely to demonstrate patient safety issues which are already implicated on reports in the WHO database. Current examples are:
  - an investigation of co-reported drugs for interactions based on known CYP enzyme metabolic interactions;
    - How many are reported as interactions
    - How many are unrecognised as interactions
    - Which drugs and which reactions are most commonly involved
    - A data mining analysis for patterns in the data e.g. demographics
    - An analysis of interactions relating to anticonvulsants
      - will include taking contact with a major patient organisation for epilepsy, and discussing their findings
  - An investigation into drugs commonly causing anaphylaxis or angio-oedema:
    - A review of possible re-exposure and cross sensitivity. This might not be easily done with the data that we have, and may point to one area of future improvement
    - A possible analysis of health care database information to follow up the pre-exposure, cross sensitivity issue in a different data set
    - An analysis of cases for CYP enzyme status (thought to be a risk factor for allergy);
  - An analysis, including data mining for patterns of the worldwide reports of anticoagulants and bleeding ADRs, and their outcomes
  - An analysis for possible interactions which might either promote, a) bleeding or, b) clotting.
  - A possible analysis of a health care dataset for patterns indicating avoidable risks
  - An analysis of vincristine and paralysis or death in the global database
  - An analysis of oxytocin for failed response and also death
  - An analysis of beta-blockers and asthma.
- Work with the volunteer national centres to produce a modified report form to capture patient safety event details (starting from the ICH E2B format).
- Work with volunteer national centres to decide on the best cause analysis tool to use in the practical situations of the national centres.
- Consider an extension of the preliminary work on paediatric adverse reactions
  - This will probably be in the area of looking at dose variations of drugs with age, comparing with information in SPCs, and whether ADR cases are especially frequently associated with high doses of drugs.
- Review five SPCs for well known cardio-vascular drugs for their merit in providing useful advice to patients and prescribers over safety issues.

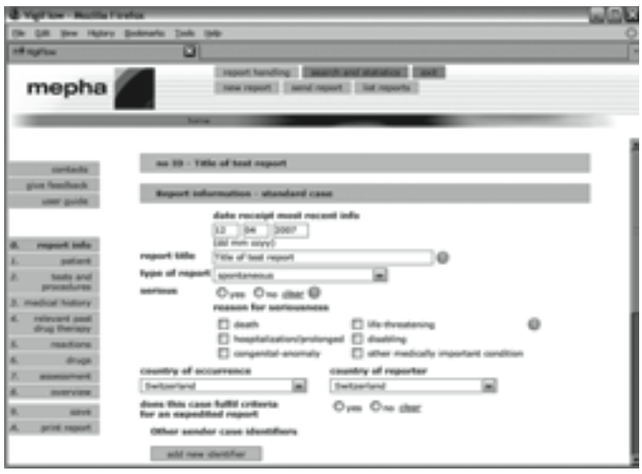
Any suggestions or further volunteer national centres should contact either Rachida Soulaymani-Bencheikh or *the* UMC.

Further Approval for VigiFlow

As was mentioned in the article in UR32 'Validating Vigibase Online', work has been on-going for about two years to make *the* UMC's ADR report management software – now called VigiFlow – suitable for use in the pharmaceutical sector. A Swiss firm, Mepha, based in Aesch near Basel, develops and manufactures innovative pharmaceutical products, and has been a pilot user of VigiFlow for a few years, and it was partly on their initiative that the GxP validation of VigiFlow reported in UR32 was carried out.

The pharmaceutical sector and the UMC working together on VigiFlow: Magnus Wallberg (UMC), Nathalie Cambon, Simone Weibel and Magali Genevray (Mepha), and Jessica Nilsson (UMC)

In December 2006 Mepha sent two representatives to *the* UMC to carry out an audit of the validation of VigiFlow. Paul Brotschi and Thomas Häuptli spent two days at *the* UMC and asked numerous questions. All aspects of VigiFlow were scrutinized thoroughly; the main focus being the development, testing and documentation. The questions the auditors asked underlined the importance of high security when logging onto the system, the significance of backing up the data and testing the system consistently.



We have now received the final report and conclusion from their audit. We are delighted that *the* UMC has been approved as suppliers of VigiFlow to Mepha. There are a few items to be implemented, such as allowing no more than five incorrect attempts to log in (to reduce the risk of hackers gaining entry to the system). The plan is to implement the changes Mepha requests in the next version of VigiFlow.

GxP is the generic term for the set of 'good practice' requirements in widespread use in the pharmaceutical industry, eg Good Laboratory Practice, Good Clinical Practice, Good Manufacturing Practice, Good Distribution Practice. The key to validation under 'GxP' is documentation, so companies must prove that the software and systems they use work according to the specification needed and are used as such.

UMC at DIA in Japan

At the 9th DIA Annual Workshop for Clinical Data Management in Tokyo, Japan on 29-30 January Marie Lindquist and Anders Hansson represented *the* UMC and there was a stand where the WHO Drug Browser was demonstrated. The brochure 'WHO Drug Dictionary & Co' was released in Japanese to coincide with the meeting, and Anders Hansson spoke on "How to choose the best format of the WHO Drug Dictionaries to meet both good data entry procedures and enable powerful statistical output". As in the rest of the world, many Japanese clients are interested in learning about the different dictionary formats.

Anders Hansson (back to camera) talks to delegates during a refreshment break in Tokyo.

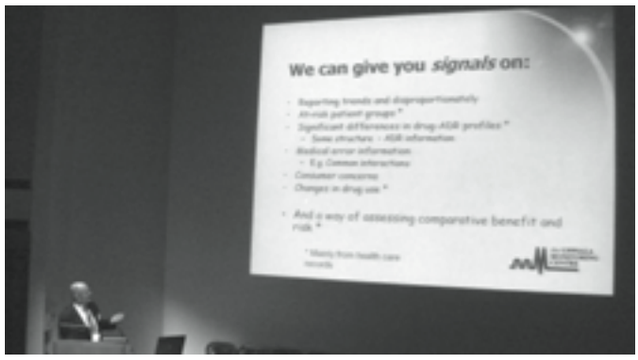
This was the second year that *the* UMC had participated in the meeting and had a stand to showcase the service we provide. This year was the first DIA meeting in Japan with parallel sessions; *the* UMC's presentation was crowded despite the parallel session being in Japanese.

Marie Lindquist, Anders Hansson, Mr Sen Sinohara (Director, Head of Product Safety & Pharmacovigilance Dept, Tsumura), Kiichiro Tsutani (Professor of Pharmacoeconomics, Graduate School of Pharmaceutical Sciences, the University of Tokyo), Dr Hiroki Takuma (Nihon University).

the UMC staff had the opportunity to meet some current clients, as well as those working in academia and regulatory authorities. The WHO Drug Dictionaries have not been well known in Japan until the last couple of years. Currently *the* UMC is investigating how to support coding and analysis in Japanese. Interesting discussions took place and the plan is to present a solution later this year.

Edinburgh conference on clinical safety

Ralph Edwards was the key-note speaker at a one-day conference in Scotland organized by the Royal College of Physicians of Edinburgh in February, 'Improving Clinical Effectiveness and Patient Safety'. The four sessions focused on 'Achieving Maximum Clinical Effectiveness', 'The Safety of Drugs in Clinical Use', 'Improving Safety of Medicines in Practice: Problem Drugs' – this had an overview of hospital practice, followed by a closer look at insulin, anti-coagulants and opioids – and lastly 'Medication Errors and Strategies for Prevention'.



Ralph Edwards lecturing at the Royal College of Physicians of Edinburgh

Ralph Edwards, giving the 'Stanley Davidson Lecture', spoke about the WHO's international work of collecting and collating adverse drug reaction signals at *the* UMC and illustrated his talk with both problems and successes. While acknowledging that individual case safety reports (ICSRs) reflect biases, prejudices, misdiagnoses and impressions, he pointed out that they also contain important information about true rare events, about drug interactions, unusual patient phenotypes and that with modern methods of knowledge finding they are a valuable source to pointing up suspicions of drug adverse reactions. He also called for more patient involvement in decision-making and more independent funding of medicines safety.

The event was graced by the presence of Professor David Finney, a reprint collection of whose writings was recently published by *the* UMC, and Ralph was able to present a copy of this book to the Royal College.

National Conference in Poland

Anna Arcab reports

The issue of drug safety and pharmacovigilance is becoming more important in Poland. There are several initiatives to encourage healthcare professionals to share their experiences of observed ADRs. This is the very first step to identify certain signals, and after gaining more data, these signals may be confirmed as adverse reactions.

The Polish health authorities organized a conference dedicated to drug safety on the 8th of March 2007 in Warsaw. Of the 600 attendees at the conference, some participants came from other cities and some from other countries. The Polish Vice-Minister of Health, Mr Bolesław Piecha opened the meeting, asking all the attendees to co-operate in the field of pharmacovigilance. The session was chaired by the Vice-President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Dr Elzbieta Wojtasik. Then the President of Office, Dr Leszek Borkowski underlined the importance of drug safety issues. The speakers were prominent experts from the Polish regulatory agency, the Uppsala Monitoring Centre (Dr Ronald Meyboom), academia and the pharmaceutical industry.

Dr Leszek Borkowski - President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, Dr Joerg Hasford and Dr Ronald Meyboom

The introductory presentation was given by Dr Agata Maciejczyk, the head of Pharmacovigilance unit within the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. Dr Ronald Meyboom then spoke about different aspects of signal identification, and presented the Uppsala Monitoring Centre as the centre where the huge amount of data is gathered, collated, organized in the WHO database and from where it can be retrieved when needed. The possibility of signal identification by statistical methods is of great importance, as well as the dissemination of information to all the national participating centres. There was also a very interesting lecture by Professor Joerg Hasford of Ludwig Maximilians University in Munich. His talk was based on the experience of a German project, gathering information on ADRs using epidemiological tools. Professor Hasford presented data which had been elaborated and analyzed by his team.

The large, attentive audience in Warsaw

Presentations by the speakers from pharmaceutical companies referred to the importance of obtaining data from pregnant women which may be done only by reports from spontaneous monitoring (Dr Pawel Kapuściński, GSK representative). A presentation describing the new risk management tool – Risk Management Plan - was given by Dr Maria Grazia Zurlo from Pfizer. The speaker from J&J (Dr Ludo F Lauwers) described the role and responsibilities of the European Qualified Person for Pharmacovigilance (QPPV), from his own experience as the nominated EU QPPV.

The last part of the conference was dedicated to Polish regional centres based in medical universities and established independently. They started to operate, because in every centre there was a person, a pharmacologist, dedicated to the problem of drug safety. The leaders of the three centres – Professors Anna Jabłecka from Poznań, Anna Wiela-Hojeńska from Wrocław and Dr Jarosław Woroń from Cracow – presented their scientific achievements.

The conference was planned to be a one-day meeting, but there were really a lot of important messages to take in for all the attendees as well as for the team of Pharmacovigilance Unit in Poland.

A pharmacovigilance website for India

A newly-opened website created by Dr Bhajish B and Mr Naveen Raju, MSc students in clinical research at the Institute of Clinical Research (India) in Bangalore, offers a comprehensive view of pharmacovigilance and practical information. The two webmasters' stated objective is "creating awareness among healthcare professionals in India about the importance of adverse drug reaction reporting". The idea for it originated from a study among doctors in Bangalore city which found that the most important cause for not reporting ADRs was not being aware of the national pharmacovigilance programme of India. "We decided to start a website to create awareness about importance and methods of ADR reporting aimed at healthcare professionals".

The site contains details about the importance of pharmacovigilance, details about the national pharmacovigilance programme of India, how and to whom to report ADRs, basic procedure of causality assessment and information about drug information centres in India.

Future plans include to give links to important national and international pharmacovigilance and regulatory sites, ADR bulletins and to create a forum for all pharmacovigilance professionals in India to interact, network and discuss relevant issues in pharmacovigilance. Dr Bhajish says "We intend to create awareness as long as possible for the betterment of human health!". The site is a great initiative and worth a visit even for those living outside India.

www.pharmacovigilance.co.in

...and a celebration of pharmacovigilance:

Dr Bharat Gajjar, Associate Professor of the Department of Pharmacology at Pramukhswami Medical College (Gujarat) in India organsed a pharmacovigilance week to increase awareness regarding reporting of adverse drug events among health care professionals from 25th to 31st March 2007. As well as poster and essay competitions for medical, physiotherapy and nursing students, the full week of activities included a quiz for medical teachers, daily talks for all teachers, students, and private practitioners, a daily bulletin during the week and print and electronic media outreach.

Spreading the word

Thai pharmacy students get the communications skills message

Undergraduates in the Faculty of Pharmacy at Rangsit University, near Bangkok, Thailand, have had a new unit added to their five-year curriculum: communication skills for pharmacists. The five-day course probably represents by far the most serious commitment to this important area of learning in the whole of Thai healthcare education – and is considerably more than many medical, nursing or pharmacy students are exposed to anywhere in the world.

The course covers all the basic skills of communication (listening, questioning, exercising empathy, and so on), as well as skills for special circumstances such as community pharmacy dispensing, inpatient and critical care, terminal illness, discharge counselling; risk communication, negotiation, public health campaigns, managing meetings – and much more. Not only must students master an entirely new area of learning and skill, but they must also cope with being taught in English, even if with some help from a talented bilingual student as interpreter.

The visiting lecturer is Bruce Hugman, *the* UMC's own communications expert, whose home is in Thailand. He has delivered two of what will now be regular annual courses.

"It's been a real challenge on all fronts" he says. "Not only must I communicate complex ideas and skills effectively, but to students with varying competence in English, who are very unused to the level of interaction and participation I demand. And there are about 180 of them!"

It's clear, however, that whatever the potential obstacles, the courses have been very warmly received by students and the level of participation and degree of entertainment have been considerable.

The huge class of third year pharmacy students at Rangsit University at the end of their five-day course in communication skills. "They were a delight to teach!" says Bruce Hugman , fourth row from the front.

It's to the credit of Head of Department, Ajarn Oraphan P. Matangkasombut, and the two course directors, Ajarn Apinnee and Ajarn Sasiporn, that they have had the vision to include this neglected area on an equal footing with the rest of their students' training.

Your ideas on communication skills

Can you help?

the UMC's communications guru, Bruce Hugman, has recently signed a contract with the UK-based Pharmaceutical Press for a book on communications knowledge and skills for healthcare professionals, particularly pharmacists, nurses and doctors. It's scheduled for publication early in 2009.

Bruce is keen for the book to reflect the real-life experience and priorities of as many workers in healthcare as possible, and he's asked Uppsala Reports for the chance to seek help from our readers.

"Ideas and suggestions from readers of Uppsala Reports would be really wonderful," Bruce says. "Particularly useful would be examples of situations in healthcare where communications are challenging or unusual – with patients or colleagues in hospitals, clinics or pharmacies."

"The book will be a practical handbook for students and practitioners, so any thoughts about the priority knowledge and skills in communications that will help improve relationships with patients and the effectiveness of therapy will be especially useful – and that includes the issues from patients' perspective as well, of course," he adds.

Bruce promises that he will respond personally to anyone who is kind enough to offer suggestions or support, and there will be a proper acknowledgement of contributions in the book.

You can contact him at: mail@brucehugman.net. There is also a page on his website describing the project in more detail: www.brucehugman.net.

Recent visitors

Sten Olsson reports

The editor of a popular book on drug safety methodology about 25 years ago expressed the view that it was unfortunate that the co-ordinating centre of the WHO International Drug Monitoring Programme had been moved to a "remote corner" of the European continent. At the time this statement was of some concern to us working at *the* UMC, but a quarter of a century later, we do not feel that we have suffered from operating in isolation, far away from our partners. *the* UMC partners are spread all over the globe, and there is no particular location that would be more or less central geographically. It seems that Uppsala is not such an isolated place after all, because we quite often have the opportunity to welcome to our offices colleagues from national pharmacovigilance centres or other associates who are passing by and just stop over for a few days or hours.

Bernardt Sachs and Ulrich Hagemann of BfArM at the UMC

Germany

On 13 February Ulrich Hagemann and Bernardt Sachs from the pharmacovigilance division of the German regulatory agency BfArM spent a few hours at *the* UMC. They thought that visiting us was a natural follow-on from a meeting they had earlier had with the Swedish Medical Products Agency, also located in Uppsala.

USA

On 30 March we had a short visit from Michael Cohen, USA, president of the Institute of Safe Medication Practices, ISMP (www.ismp.org). Dr Cohen and the Institute have a more than 30-year long history in trying to prevent medication errors in the USA. He is the co-editor of the bi-weekly newsletter ISMP Medication Safety Alert!® with 640,000 readers in the United States, and the author of the book Medication Errors.

Johanna Strandell at *the* UMC gave him a presentation of the main UMC operations and of the pilot project on patient safety that *the* UMC has just started in collaboration with the World Alliance for Patient Safety. Dr Cohen is a member of the Advisory Committee of this Alliance. It was concluded that ISMP and *the* UMC have many reasons to exchange information and work more closely together in the future towards the common goal – safer use of medicines for all patients.

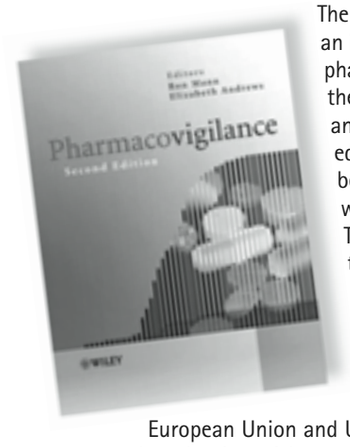
Pharmacy students

In March *the* UMC was also visited by about 15 pharmacy students who have chosen the five-week course in the MSc programme on Adverse Reactions and Pharmacovigilance that *the* UMC is running in collaboration with Uppsala University. It was the third consecutive semester this course was offered and interest among the pharmacy students is growing.

Pharmacovigilance, 2nd Edition

ISBN: 978-0-470-01803-3
Hardcover, 702 pages, January 2007
Ronald D. Mann, Elizabeth B. Andrews (Editors)
Publisher: John Wiley & Sons Ltd.

The first edition of Pharmacovigilance came out in 2002 and the new revised edition is an improvement on the first and rightly so; to reflect the significant changes in the world of pharmacovigilance within the last five years, with a cover design and typeset which are also very easy on the eye.



The list of editors and contributors makes an interesting reading of 'who's who' in pharmacovigilance and their standing in the subject gives credibility to the book and its contents. According to the editors, the main goal of the book is "to be a comprehensive volume on the whole area of pharmacovigilance". That is quite an ambitious goal. Does the book achieve its purpose?

Strangely, the editors decided to dedicate two of the first chapters in a book on pharmacovigilance to discuss its legal basis in the European Union and USA. It would seem more relevant to start the book with a patient perspective and why pharmacovigilance is needed in health care. From there on, though, the book certainly covers a lot of ground regarding recent and relevant developments in drug safety. However, the world of pharmacovigilance does not start and end in the European Union, USA, New Zealand and Japan. Conspicuously missing is the perspective from developing countries, where relevant concepts such as counterfeit drugs and other topics specific to these countries could have enriched the book. Other areas within pharmacovigilance not given much coverage in the book are herbal medicinal products and vaccines.

These topics may have been touched on briefly by various contributors but because of their significance within pharmacovigilance, they deserve to have their own chapters in the book.

True to the spirit of the hype on environmental awareness, credit should be given to the publisher and printers for using "acid-free paper responsibly manufactured from sustainable forestry in which at least two trees are planted for each one used for paper production".

Hopefully, the next edition will include the above-mentioned omitted areas and other relevant topics and then the book will pretty much achieve its purpose of being a "comprehensive book on the whole area of Pharmacovigilance".

DSRU biennial signal detection meeting

Signal detection lies at the heart of pharmacovigilance. Post-marketing drug safety monitoring systems aim primarily at identifying unexpected links between the use of a drug(s) and harmful outcomes.

The Conference on Signal Detection in Pharmacovigilance is a biennial meeting organised by the Drug Safety Research Unit (UK) since 2001. The goal of the conference is to bring forward recent advances in signal detection and discuss their place in pharmacovigilance. Over two days, speakers from academia, regulatory agencies, pharmaceutical industry and independent research organisations share results and know-how on techniques, methods under development and implementation strategies.

The 4th Biennial Conference in Signal Detection will take place on the 14-15th June 2007, at the Royal Aeronautical Society right in the centre of London. The programme includes:

- The context – epidemiological and regulatory framework
- Special therapeutic areas – vaccines and biologicals
- Data mining tools
- Implementation in small and large organisations
- Communicating signals and real-life examples.

Experts from *the* UMC, EMEA, PhRMA-FDA workgroup and the DSRU, among others, will be presenting, and it promises to be a great opportunity to learn from and interact in a pleasant and inspiring atmosphere.

Further details on the programme and registration are at: http://www.dsru.org/symposia_consensus.html

Latest WHO Drug Dictionaries News

The WHO Drug Dictionaries continue to move forward. As part of the March 1, 2007 version there are new entries, and new features:

- More than 60,000 entries have been added
- The dictionary's classification has been improved for more effective analysis
- The 2007 ATC classification has been incorporated, and products affected re-classified
- A number of product entries have been updated and errors corrected
- A new tool for versioning of the data is introduced. It can also be used for upgrading to the latest version
- The web-based WHO Drug Dictionary Browser allows direct access to the WHO Drug Dictionaries
- 'Introduction to the WHO Drug Dictionaries', a web-based course available for anyone wishing to increase their knowledge.

New entries

The March 1 version of the WHO Drug Dictionary Enhanced contains 1,095,695 entries in the C format and 185,463 entries in the B-2 format, (compared with 1,066,042 and 180,446 in March 1, 2006). The dictionary also contains 9,814 substances compared with 9,527 in 2006.

The WHO Herbal Dictionary contains 44,713 entries in the C format and 11,696 entries in the B-2 format, (compared with 11,917 and 4,443 in March 1, 2006). The dictionary also contains 2,181 substances/herbal plants compared with 1,537 in 2006.

Improved classification

the UMC has recently investigated a number of product groups, especially biologicals. These are of growing importance and their molecules are often more complex than conventional active ingredients. To allow powerful analysis it is important that the classification of these products is consistent and harmonized with that of conventional products. The coding of these groups has therefore been revised and a more consistent system has been introduced, starting with Interferons.

Consistent coding of Interferons

For 2007 the different sub types of Interferons are now treated as individual chemical entities and not as salts to one base molecule. This affects the Drug Code system since each of these will be given individual Drug Record numbers, where some previously have been treated as salts, and therefore had the same Drug Record number but different Sequence Number 1.

ATC 2007

Following the yearly revision of the ATC classification system some changes have been made in the ATC file/INA file. There are also some new ATC and Herbal ATC terms.

Cumulative changes table

A new table makes it possible to trace all Drug Codes used in the dictionary since 2004. Sometimes an entry in the dictionary is modified in a way that leads to an insertion of a new entry and the deletion of the old one. The mapping between these is part of the Changes Files. The new table makes it possible to trace deleted codes and map them to the latest version of the dictionary.

The WHO Drug Dictionary Browser

In 2006 the WHO DD Browser was launched. The Browser, with its user-friendly interface, enables direct access to all the features in the dictionary and is available over the internet, enabling immediate access starting a subscription. It can also supplement a current system which may not have the search capabilities to fully utilize the functionality offered in the browser. When there is a complicated search problem, the Browser will help find and select the product being sought.

Training

In 2006 a new web-based training course was introduced 'Introduction to the WHO Drug Dictionaries', which is available for anyone with an interest in increasing their knowledge of the WHO Drug Dictionaries.

The course offers basic knowledge about the WHO Drug Dictionaries. Each participant is introduced to the basic coding concepts necessary to record data using the dictionaries as well as how coding will affect data retrieval. On completion of the course participants will have an understanding of the content and structure of the dictionaries. This web course is also preparatory for continued classroom training.

If you have queries or need more information, you can best contact the WHO Drug Dictionary Team at drugdictionary@umc-products.com.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
23-24 Apr 2007	Reporting Adverse Events	London, UK	SMI Group www.smi-online.co.uk/smiconferences/default.asp
14-26 May 2007	Pharmacovigilance - The Study of Adverse Drug Reactions and Related Problems	Uppsala, Sweden	*the* Uppsala Monitoring Centre Tel: +46 18 65 60 60 E-mail: info@who-umc.org www.who-umc.org
17-18 May 2007	Compliance in Pharmacovigilance and the role of the EU qualified person	London, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
14-15 June 2007	4th Biennial Signal Detection and Interpretation Conference	London, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
17-21 June 2007	43rd DIA Annual Meeting, Georgia World Congress Center	Atlanta, GA, USA	DIA Fax : +1 215 442 6199 www.diahome.org
27-28 June 2007	Periodic Safety Update Reports (PSURs)	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
4-5 July 2007	Introduction to Pharmacoepidemiology	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
16-17 July 2007	Adverse Event Reporting and Pharmacovigilance	London, UK	IIR Tel: +44 (0)20 7017 7481 Email: registration@iir-conferences.com
18-19 July 2007	Advanced-level Adverse Event Reporting & Pharmacovigilance	London, UK	IIR PTI Tel: +44 (0)20 7017 7481 Email: registration@iir-conferences.com
19-22 August 2007	23rd International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Quebec City, Canada	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
31 August 2007	Pre-Satellite Workshop: Strategies In Medication Safety – Pharmacovigilance And Preventing Medication Errors as part of the 67th International Congress of FIP	Beijing, China	International Pharmaceutical Federation (FIP) www.fip.org/CONGRESS/beijing2007/index.php?id=600
16-19 September 2007	The Society for Clinical Data Management (SCDM)	Chicago, Illinois, USA	Society for Clinical Data Management (SCDM) www.scdm.org/
17-18 September 2007	Adverse Event Reporting and Pharmacovigilance	London, UK	IIR Tel: +44 (0)20 7017 7481 Email: registration@iir-conferences.com
19-20 September 2007	Advanced-level Adverse Event Reporting & Pharmacovigilance	London, UK	IIR PTI Tel: +44 (0)20 7017 7481 Email: registration@iir-conferences.com
26 September 2007	Drug Safety Surveillance	Washington DC, USA	DIA www.diahome.org
21-24 October 2007	7th Annual Meeting of ISoP	Bournemouth, UK	Hampton Medical Conferences Ltd Tel: +44 (0)20 8979 8300 Fax: +44 (0)20 8979 6700 E-mail: isop2007@hamptonmedical.com Website: www.isop2007.org

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