

# MUR 28

UPPSALA REPORTS January 2005

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

**Signal Reviewers meet together**

**Collaborations:**

**Ireland and Malta, Ghana and the Netherlands**

**Viewpoint Part 2 on the way**

**Canberra training course report**

**A view from the FDA**



# DIRECTOR'S MESSAGE



Ralph Edwards  
Director  
*the Uppsala Monitoring Centre*

In 2004 there have been a number of achievements of which we are proud. Most of these have been in our technical ability to collect, store and analyse adverse drug reaction information. The group managing our data input has worked splendidly and there are new IT developments to support our database, Vigibase, such as the web access for both input and searching: Vigibase Online and Vigisearch.

Unsupervised pattern recognition is now a reality, and thanks to collaboration with IMS Health we are now moving into a new era of drug safety knowledge-finding in databases. The Drug Dictionary team has also done wonders and we are looking forward to more developments there over next year, again working with IMS Health.

Our work in herbals has taken a substantial leap forward with the launch of a group of publications to support the rationalisation and classification of herbal substances: Guidelines for herbal ATC classification; Herbal ATC index, and, in press, Accepted botanical names and their synonyms. Along with the new WHO Guidelines on the safety monitoring of herbal medicines, these take us to a situation where we can collect data of varying levels of certainty as to the true herbal product content, in a transparent fashion: we will at least know the level of doubt about the substance(s) which might have caused an ADR. We owe Mohamed Farah and Jenny Ericsson gratitude for their persistence and commitment to the cause.

Among our efforts to explain our work, and to spread the drug safety message widely, Viewpoint Part 1 was published a couple of years ago, and has been warmly appreciated in many parts of the world. Now, Part 2 is available, and, in its sixty-eight pages, provides a detailed scientific and technical account of the WHO Programme and of our activities. While it deals with complex issues, it's presented in a way which we hope will make it accessible to a wide audience – and we need your help to send it where you think it will be useful. (See page 12 for full details.)

I do hope 2005 will be a productive and successful year for you and your colleagues. As always, *the UMC* team looks forward to maybe meeting you some time – and, we hope very much, to hearing from you when you have something to tell us or feel we can help in some way.

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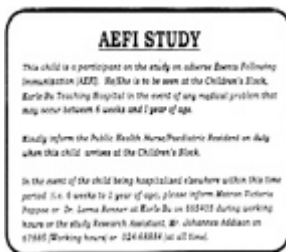
12-13

Viewpoint Part 2 is on the way, providing 68 pages of detailed, technical information about the activities, services and products of the Uppsala Monitoring Centre, particularly about the detection of signals of potential drug hazards.



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Two important collaborations between developed and emerging nations: Ireland and Malta on creating a pharmacovigilance system, and Ghana and the Netherlands on adverse events following immunization.



## 2005 Annual meeting of the WHO Programme in Geneva

At the Dublin meeting of representatives of national pharmacovigilance centres, Iran, represented by Dr Kheirollah Gholami, Associate Professor and Chair of the Clinical Pharmacy Department, Tehran University of Medical Sciences kindly invited his colleagues of the WHO International Drug Monitoring Programme to come to Tehran, Iran for the 28th annual meeting in 2005.

However, subsequently the WHO Headquarters' security office, on the basis of an assessment of the political developments in the world, recommended that WHO meetings should not be convened in Iran for the time being. Consequently the 28th annual meeting will instead be held in Geneva, Switzerland from 26 -29 September 2005.

We sincerely hope that it will be possible to hold the meeting in Iran in the near future.

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## Double helpings in Dublin



Pat O'Mahony (CEO, Irish Medicines Board), Niamh Arthur, Ralph Edwards, Mary Couper and Vladimir Lepakhin (WHO)



Participants watching a presentation of Vigibase Online during a break in the meeting



A session of the 27th Annual Meeting in progress

Last October the Irish Medicines Board (IMB) hosted and organised the 27th Annual Meeting of Member Countries of the WHO Programme for International Drug Monitoring, as well as the ISoP Annual Scientific Meeting which succeeded it, in Dublin – Ireland's historic and vibrant capital.

Seventy representatives from forty countries of the WHO Programme from all regions of the world, including Nigeria and Malta, the most recent members, attended the WHO meeting. The main topic was focussed surveillance methods but sessions also looked at latest developments in pharmacovigilance around the world, and drugs of current interest.

### Focussed surveillance

Dr David Coulter, former head of the New Zealand Intensive Medicines Monitoring Programme (IMMP) gave an exhaustive background to the use of cohort event monitoring as a vital way of enforcing spontaneous reporting and giving an extra dimension to pharmacovigilance.

There was general acceptance that focussed surveillance was an important priority in improving drug safety knowledge. However, there were problems in many countries with regard to resources for such relatively intensive activity and where spontaneous reporting itself still needed strengthening and development. Working groups also examined the question of registries and their usefulness and discussed pharmacovigilance planning in relation to ICH E2E.

### A broad agenda

Other highlights were a session entitled 'Wild ideas for preventing ADRs' (exactly what the title said), and a cogent and inspiring exposition of 'Pharmacovigilance in Ireland' by Niamh Arthur with strong emphasis on scientific collaboration. Delegates had a presentation on the World Health Assembly resolution on HIV/AIDS treatment and care, and the international course on antiretroviral safety monitoring, in September in Pretoria.

Reports included the WHO International Alliance for Patient Safety, the collaboration between the UMC and IMS Health to enhance the WHO Drug Dictionary content and capability, and ICH developments.

A number of important new publications were presented to the meeting. The WHO Guidelines for the safety monitoring of herbal medicines (just printed) were handed to delegates, along with the Herbal ATC Index and Guidelines from the Uppsala Monitoring Centre.

Drugs of current interest are prepared by national delegates and presented to the whole group for comments and feedback. In Dublin the topics were:

- Phenylpropranolamine
- Polygeline
- HMG – CoA-reductase inhibitors
- Levonorgestrel-releasing intrauterine device
- Dutasteride
- Cabergoline
- Reboxetine
- COX-2 inhibitors
- Counterfeit medicines
- Brivudine
- Amodiaquine and Lapdap
- BCG vaccine of SSI strain
- Hepatitis B vaccine

### ISoP's annual get-together

Following on straight after was the ISoP Annual Meeting, which was the traditional sampling of challenging lectures and clinical research reports from Europe and beyond. In a joint session with the WHO, delegates heard a call for more innovative analysis tools, particularly the use of data-mining, in a keynote speech from Stephen Evans. In the closing session, Sir Michael Rawlins, (chairperson of the UK's National Institute for Clinical Excellence) – said that drug regulation must become more open and focussed on the needs of patients and society. He proposed widening the view on evidence away from a concentration on p-values to a broad view on evidence of all sorts, and moving from considering just efficacy in narrow clinical trials on the one hand, and solely qualitative judgements on the other.

Given that ISoP currently has an Italian as President (Giampaolo Velo), it must have been pleasing for him to witness so many impressive contributions from colleagues in Italian regional centres and universities, including Messina and Verona.

The poster prize winners were 'Spontaneous reporting of ADRs associated with herbal medicines: a cross-sectional survey of national pharmacovigilance centres' by J Barnes and A Aggarwal, 'Agreement of expert judgment in assessment of causality of adverse drug reactions' by Y A Arimone, B B Bégaud et al, and 'Neurological disorders associated with vaccine use: a prospective case-control study' by G Traversa, A Capuano et al.

In all, two fine meetings, for which Niamh Arthur and her thoughtful colleagues from the Irish Medicines Board must take much credit in the high standards for both meeting organisation and in the enjoyable content, and all-important social gatherings.

# Nepal new Associate Member

*Sten Olsson reports*

The Ministry of Health in Nepal has now applied for their country to be admitted to the WHO Programme for International Drug Monitoring, as an associate member country.

The responsible person is

Mr Bimal M Shrestha  
Department of Drug Administration  
Drug Information Division  
Bijulibazar, Newbaneshwor  
Kathmandu, Nepal  
Tel: +977-1-4780227  
Fax +977-1-470572  
E-mail: dda@healthnet.org.np

I met Bimal Shrestha for the first time at an ISDB (International Society of Drug Bulletins) meeting in Berlin in October 2003. We have maintained e-mail contact on and off since then. In June *the UMC* had a visitor from Nepal, Mr Prinaya Mishra, who came for a day from Copenhagen where he is doing his PhD. Prinaya and Bimal have since organized a pharmacovigilance conference in Nepal and managed to convince the authorities that they should be involved in drug safety monitoring. The Ministry has yet to allocate resources for the activity, but the department in Kathmandu is now in our network.

## Indian National Programme inaugurated

The reinvigorated Indian National Pharmacovigilance Programme was inaugurated on 23 November 2004 in New Delhi *reports Brijesh Regal*. The Health Minister formally initiated the programme in the presence of several senior health officials. Co-ordinators from 50 pharmacovigilance centres across the country participated in the two-day workshop to grasp the operational nuances of the national pharmacovigilance protocol so that the programme operates in a harmonized manner.

For many involved in the setting-up of this programme, it has been a long and arduous journey lasting more than three years; finally, perseverance has prevailed! It is hoped that the National Programme will bring pharmacovigilance in India forward across the whole country and that dedicated and efficient leaders will emerge in the times to come. This will ensure a sustained and viable pharmacovigilance programme to provide plentiful data for the WHO database.

The contact person for the Indian national pharmacovigilance programme is:

Dr Ashwini Kumar  
Drug Controller General (I)  
342 Nirman Bhawan  
Ministry of Health and Family Welfare  
Govt of India, New Delhi 110 011, India  
Tel: +91 11 2301 8806  
E-mail: dci@nb.nic.in

### Indian development initiative

The WHO regional office in New Delhi (SEARO) has taken the initiative to organize a training workshop in Mumbai (Bombay) 17 - 21 January, 2005, to support the early development of the new Indian pharmacovigilance system. The local organizer is Dr Urmila Thatte at the Mumbai regional centre. Managers of the zonal, regional and peripheral centres from all over India will participate at the workshop. The WHO Programme will be represented by Mary Couper, WHO-Geneva and Sten Olsson from *the UMC*.

### Nigerian Inauguration

Uppsala Reports 27 featured an article on Nigeria joining the WHO Programme. A full report of the inauguration is now available on *the UMC* website under Promotion & Training > Presentations/posters describing national pharmacovigilance activities.

Mary Couper, Medical Officer, Quality Assurance and Safety of Medicines, Essential Drugs and Medicines Policy, World Health Organization, reports on two recent meetings



ICH group in Yokohama

## A view from WHO

### Pharmacovigilance Planning: An important new guideline for the ICH

The decision to approve a drug is based on its having a satisfactory balance of benefits and risks within the conditions specified in the product labelling. This decision is based on the information available at the time of approval. However, the product is often used in settings different from clinical trials and a much larger population might be exposed in a relatively short timeframe.

Once a product is marketed, new information will be generated, which can have an impact on the benefits or risks of the product. Detailed evaluation of the information generated through pharmacovigilance activities is essential for all products to ensure their safe use.

The new E2E guideline is intended to aid industry and regulators in planning pharmacovigilance activities, especially in preparation for the early post-marketing period of a new drug. The guideline describes a method for documenting risks and proposes a structure for a pharmacovigilance plan. It consists of two parts: the Safety Specification, which outlines the main risks identified in clinical trials, and the Pharmacovigilance Plan, which details the proposed actions to be undertaken in addressing these risks. It should be remembered that routine pharmacovigilance activities are all that is required for some products. There is also an annex providing details of methods which can be used in pharmacovigilance.

This guideline will be of immense benefit to public health programmes throughout the world as they consider new drugs in their countries.

### Safety Advisors for WHO

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its second meeting in October 2004. This Committee provides advice to the Director General of WHO on pharmacovigilance policy, and issues related to the safety and effectiveness of medicinal products.

One of the major priority areas was the launch of the World Alliance for Patient Safety. The Committee participated in this activity by means of a video-link with the event taking place in Washington. The Advisory Committee will work closely with the Alliance particularly in reporting medication errors and conducting research on the impact of safety measures.

The issue of safety of medicines in children with emphasis on off-label use was also discussed. The Advisory Committee recognized that this is an important and neglected area that should be brought to the attention of WHO.

The Committee welcomed the opportunity to collaborate with the Expert Committee on the Use and Selection of Essential Medicines. It offered to review safety issues for new applications of products for the Essential Medicines List as submitted by the secretary of the Expert Committee.

Specific medicines evaluated included the anti-retrovirals tenofovir and emtricitabine. It was decided that it was too early to have a full picture of the toxicity of these medicines. An enquiry into the safety of kava has also been commissioned.

The Committee also heard various reports from the public health programmes in WHO and discussed how pharmacovigilance could best be incorporated into these programmes.

### Changes at WHO Headquarters

The current Department of Essential Drugs and Medicines Policy is reorganized into two departments, one responsible for policy, norms and standard setting and the other for technical cooperation and traditional medicine.

- Dr Hendrik Hogerzeil is appointed as Director, Department of Medicines Policy and Standards. Dr Hogerzeil, a national of Netherlands, is currently Coordinator of what is now Policy, Access and Rational Use, Department of Essential Drugs and Medicines Policy.
- Mrs Malebona Matsoso is appointed as Director, Department of Technical Cooperation for Essential Drugs and Traditional Medicine. Mrs Matsoso, a national of South Africa, is currently Chief Director and Registrar in the Department of Health of South Africa.
- Dr German Velasquez is appointed as Associate Director, Department of Technical Cooperation for Essential Drugs and Traditional Medicine, effective immediately. Dr Velasquez, a national of Colombia, is currently Coordinator, Drug Action Programme, Department of Essential Drugs and Medicines Policy.

# China's first national drug safety conference

*Bruce Hugman reports from Shanghai and Beijing*

## Shanghai meeting boosts pharmacovigilance across the country

Shanghai's International Convention Centre was the venue for China's first national conference on pharmacovigilance and pharmacoepidemiology, held from 20-22 November, 2004.

About two hundred participants, from all thirty-one provinces and the national centre attended the meeting, along with a number of senior national and regional officials.

Topics on the two-day agenda included

- international developments in pharmacovigilance and the WHO Programme
- national ADR monitoring strategy
- the current state of pharmacology, toxicology and pharmacoepidemiology in China, including research developments
- safety aspects of antibiotics, anti-hypertensive drugs and the injection of Chinese medicines
- Chinese medicines
- Crisis management in drug safety.

The international perspective was represented by Dr David Coulter from the New Zealand Intensive Medicines Monitoring Programme, and Bruce Hugman, UMC consultant.

David Coulter gave presentations on international developments in pharmacovigilance and on Vigibase (the WHO ADR database); Bruce Hugman spoke about effective communications methods and crisis management in drug safety. Their presentations were simultaneously translated into Chinese by a very hardworking Dr Zhu Chouwen from Fudan University.

## ADR monitoring given new impetus

The conference was planned to strengthen ADR monitoring and drug safety activities throughout the country. In 2003 the annual reporting rate for China was 30,000 ADR reports - the rate is increasing each year. These have accumulated since China formally put ADR monitoring in place in 1999. Reporting has since been made mandatory and the hope is that the number and range of reports will increase significantly in the coming years.

China joined the WHO Programme for International Drug Monitoring in 1998. Currently, discussions are in hand with the UMC to translate many more Chinese reports so that they can be entered into Vigibase. With so great a population, and such a very long history in the use of traditional medicines, China has a particularly important and unique contribution to make to the overall picture of global drug safety.

## Activity in the Shanghai regional centre

The Shanghai centre is responsible for about 6,000 of the nation's ADR reports. It's a record Dr Du Wenmin, Vice Director of the centre, is proud of and one on which he hopes to build. While paper forms are available, about 60% of reports are submitted electronically. He is currently also assembling a cohort of 300,000 patients in the city with linkage to hospital records, to extend the centre's surveillance activities.

## Visiting the National Centre

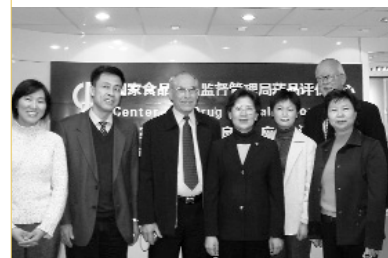
David Coulter and Bruce Hugman were invited by the Director of the National Centre, Professor Liya Cao, to visit and conduct a seminar with members of her team. David led a discussion about causality assessment and signal detection, while Bruce dealt with communications and media relations.

It was evident that there was great determination to increase the range and effectiveness of ADR reporting throughout the country. Currently, there are collaborative projects with Canada and France, with a focus on the safety and monitoring of traditional medicines.

On behalf of the WHO Programme and the UMC, David Coulter and Bruce Hugman expressed the hope that China would take an ever-increasing part in the WHO Programme, offering its experience and knowledge for the benefit of the rest of the world.



*Ren Dequan, Vice President of the State Food and Drug Administration (centre) with senior members of the National Centre and the Shanghai Centre, including Dr Du Wenmin (second from left), who was the inspiration behind the organisation of the conference, David Coulter and Bruce Hugman*



*The National Centre - Professor Liya Cao, Director (centre) with Chen Yixin (Associate Director) to her right and other senior members of the team with David Coulter and Bruce Hugman*



*Education in the Temple of Heaven: in the extensive, quiet gardens of the Temple of Heaven, there are rows and rows of posters providing sound health advice for the people of Beijing on everything from good diet to relaxation and meditation. Here the guide, Eddie, discusses one of them with Yang Le from the National Centre and David Coulter.*

## Course participants

Mr Enoch Ampratwum, Ghana  
Ms Sun Jun, China  
Mr Richard Rukwata, Zimbabwe  
Mrs Akudo Amaeshi, Nigeria  
Miss Comfort Suku, Nigeria  
Dr Sharon Sime, New Zealand  
Dr Shahram Ejtemaei Mehr, Iran  
Mr Ibrahim Ali, Nigeria  
Dr Shahram Ala, Iran  
Mrs Amelia Lela, Indonesia  
Mr Apolosi Vosanibola, Fiji  
Ms Nguyen Hong Nhung, Vietnam  
Dr Nanjaa Tsogzolmaa, Mongolia  
Mr Ugyen Dendup, Bhutan  
Dr Shalini Sri Ranganathan, Sri Lanka  
Mrs Shirley Gaiyer-Kore, Papua New Guinea  
Ms Theresa McGarry, Australia  
Ms Tina Mason, Australia  
Dr Dominic Barnes, Australia  
Mr Theo Giannou, Australia  
Ms Serene Goh, Australia  
Dr Jenny Hamilton, Australia  
Dr Che Yan, Australia  
Dr Li Joy, China

*The course group photo*



# Springtime for Training

*Bruce Hugman reports from Canberra*

In November 2004, more than twenty participants from fifteen countries spent two weeks hard at work in Canberra, Australia's capital, on the UMC's training course. This was the second time that the Therapeutic Goods Administration (TGA) had hosted the course (previously in 2002). Again it was held in the TGA's spacious and attractive building and benefited from the usual high levels of Australian efficiency and hospitality.

All participants took Module 1 (the general principles and practice of pharmacovigilance), and the great majority stayed on for the challenges of Module 2 (pharmacoepidemiology). Under the leadership of John McEwen, Principal Medical Adviser at the TGA, and his team, with a number of distinguished visiting lecturers, the demands on students were considerable, 8.30 to 5 every day, five days a week. The UMC was represented by Sten Olsson, Andrew Bate, Jenny Ericsson and Bruce Hugman.

## A rich mix

Many participants came from countries already members of the WHO Programme, and there were also a handful of drug safety specialists from the pharmaceutical industry. They were maybe new in their jobs in pharmacovigilance or were already working but without a background of intensive training. Some were from countries with infant ADR monitoring systems, slowly building national awareness and reporting towards achieving membership of the WHO Programme. Some were more experienced, but looking for additional knowledge and skills, especially in

pharmacoepidemiology. Nigeria, at the time one of the newest members of the Programme, was strongly represented with three of the national team.

All participants came from Africa and the Asia-Pacific region, demonstrating the attraction of the course being held out of Europe from time to time. The geographical range spanned Nigeria to Mongolia to New Zealand and many places in between, including Bhutan – population around 600,000 – a country many participants had, shamefacedly to admit, they need help to find on the map. Hearing about the dynamic modernisation of Bhutan (as well as its location) was among the rich educational experiences of the gathering.



*Members of the course faculty on the TGA's modern art: Jenny Ericsson, Sten Olsson, Andrew Bate and John McEwen (front)*

## Time off

At lunchtimes participants were able to walk around the TGA building – set in countryside on the edge of the City – spotting wild kangaroos and enjoying the warm spring sunshine. The TGA hosted two dinners, one at a splendid Turkish restaurant and the other in the romantic setting of the lakeside, with the city lights twinkling across the water as darkness fell. These and other informal events helped to cement the many new friendships made across the nations.

## Verdict

While many felt – as others before them have done – that the schedule was demanding and intense, there was universal approval of the course. It was felt that it would greatly enhance participants' pharmacovigilance practice and contribute to the development of countries' efforts in drug safety. However, as the course had more participants with an industry background than earlier courses, some thought that the sessions dealing with establishing a national pharmacovigilance programme were less relevant to them, which is not surprising. The main focus of the training is from a public sector perspective.



## the UMC – TGA Canberra course in pictures



Course members on the TGA steps with Ian Boyd (TGA) second from left



'Hands-on' training: inputting in Vigibase Online, and searching the WHO database



Hong Nhung Nguyen (Vietnam) receives her certificate of participation from Sten Olsson (UMC) and John McEwen (TGA)

# The next UMC training course

the Uppsala Monitoring Centre is pleased to announce its tenth international pharmacovigilance training course, to take place in Uppsala, Sweden from 23 May – 3 June 2005. Previous courses, held from 1993 to 2004, have been represented by participants from over 85 countries.

To satisfy the requirements of professionals with slightly different needs the course is divided into two separate modules, and for 2005 will have an option for the second module:

### Module I: Introduction to ADRs

- Spontaneous adverse reaction reporting
- Setting-up and operating a centre for spontaneous adverse reaction monitoring
- Case evaluation – causality assessment
- Terminologies used in adverse reaction monitoring
- Use of computer systems in recording and interpretation of ADR information
- The WHO Programme
- ADR information from the medical literature.

### Module II can be taken as either

- a) Introduction to pharmacoepidemiology – with the aim of making participants familiar with the basic concepts of pharmacoepidemiology and to enable them to read and analyse results from epidemiological studies with a critical mind;
- or,
- b) Effective Communications in pharmacovigilance – focusing on the skills and practice of effective communications for pharmacovigilance professionals.

Attendees choose to attend Module I or Module II, or both modules; applicants attending Module II must choose one of the options a) or b).

Theoretical and practical aspects of adverse drug reactions and pharmacovigilance are covered. The theoretical parts include lectures as well as group discussions and poster presentations by course participants. Practical sessions include recording of case information and computerised retrieval of information from the database of the WHO Programme for International Drug Monitoring.

Anyone interested in taking part should access the downloadable information from [www.who-umc.org](http://www.who-umc.org) > Promotion and Training. Participants must find funding themselves for their attendance.



Heather Rockwell (TGA) and Ugyen Dendup (Bhutan). Heather provided the most amazing range of support services for the course – from typing and photocopying, to tour-guiding, flight-booking, banking, shopping and managing the complex international communications demanded by professionals away from home: a godsend to everyone!



Ian Boyd teaching the whole group

## Reviewers meet in Uppsala

Early detection of signals of international drug safety problems is the most important task for the Uppsala Monitoring Centre. With over 3.1 million ADR reports in the WHO database (Vigibase) an automated procedure of identifying drug-ADR combinations for further assessment is a necessity.

Since the fourth quarter of 1998 *the UMC* has been using the BCPNN 'data-mining' methodology to produce quarterly line listings of drug-ADR combinations that stand out statistically from the background of all reports in the database – so-called 'associations'. First these are checked at *the UMC* for occurrence in the available product information literature. For drugs where the reaction is not found or not described well enough, case reports are retrieved from the WHO database. *the UMC* then sends the cases to the most appropriate expert in the review panel to assess the evidence for the reaction being related to the suspected drug using their clinical experience and pharmacological knowledge.



*Intense discussion in the plenary sessions*

### The expert review panel

As well as the use of sophisticated computer systems and algorithms, clinical knowledge, experience and interest, often together with a signal-instinct or intuition, are unique human qualities which cannot be replaced by computers: clinical review is of immense importance in signal detection. *the UMC* has an international expert review panel consisting of 36 consultants from twenty countries. Each member of the panel reviews combinations belonging to one or more areas appropriate to their professional field. Analysis of potential signals includes checking the available case data and making literature searches, using their clinical experience and knowledge. After assessing the cases, including judgment on the causal strength of the drug-ADR association, the reviewer drafts a short report if he or she finds the issue worth notifying to national centres in the WHO Programme. After review within *the UMC*, the text of this report may be included in the document 'Signal' for distribution to national centres.

The review team contains experts in herbal and traditional medicine. Some play an important part as co-authors with UMC staff in scientific publications.



*Members of the UMC signal review panel and UMC staff in a relaxed work group session*

### Winter meeting in Uppsala

For the first time since 2001, most of *the UMC* Signal Reviewers met together on 13-14 December 2004 for two days of planning and updating. The aim of the meeting was for reviewers to share experiences of signal detection work and to learn how to make best use of the information in the WHO database (Vigibase), leading to a more harmonized approach to signal detection and both higher quality and increased number of signals presented in 'Signal'. The group, some of whom only became reviewers since the last meeting was held, assembled the evening before for a traditional Swedish Lucia (Christmas) concert and light evening meal.



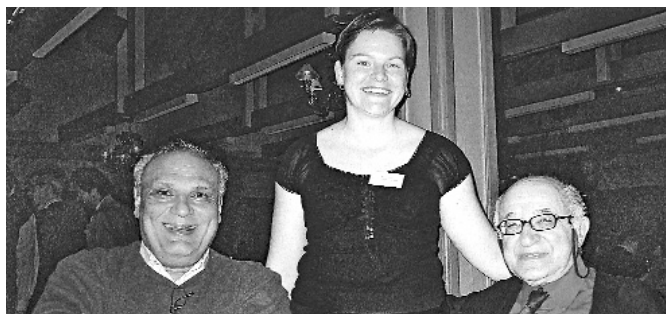
*Dr Kuruvilla, Alice Kuruvilla, Ana Maria Nunes, and Alain Rohan at the Christmas dinner.*

### Packed work sessions

On the Monday they got down to work. After introductions from Ralph Edwards, in which he expounded a key dilemma: balance between quickly finding early signals and having enough data, ie quality and meeting the key signal criteria (international, important for public health, timely, and justified), and from Marie Lindquist – an overview of the history of international signal generation within the WHO Programme, there were presentations from *the UMC's* signal team. Anne Kiuru presented an overview of the signal detection process of *the UMC* and some parts of the review panel process, then Johanna Strandell presented the 'triage system' by which associations are chosen along with some recent statistics on both UMC activity and that of the review panel. Malin Ståhl continued with the evaluation of the triage system (well-

received by the reviewers with experience of the previous system) and the need for additional triages, and Kristina Star spoke about follow-up for pending signals as well as already signalled associations. Mohamed Farah talked about classification of herbals/traditional medicinal products, followed by a presentation on the signal detection process within herbals.

Last speaker before lunch on the first day was Andrew Bate talking about the BCPNN methodology and the advantages of using Bayesian rather than classical statistics for signal detection. He concluded that the BCPNN is a tool to enhance, not replace, the signal detection process at *the* UMC.



Saad Shakir, Anne Kiuru and Ed Napke. Anne Kiuru was the 'mastermind' behind the organisation of the Signal Reviewers meeting.

During the afternoon the reviewers debated issues relating to their work and finished with Ronald Meyboom who made a short presentation of how he performs his review task.

In the evening a traditional Swedish Christmas dinner was taken by signal reviewers and UMC staff at the 'Markan' pavilion at Eklundshof, just outside the city.

### In-depth discussions

Tuesday opened with a session on the contents of Vigibase from Helena Sjöström, showing some reporting statistics from the different member countries. She also demonstrated the web-based case management system Vigibase Online. Erica Walette explained the structures of the WHO-ART and WHO-DD and demonstrated how to make searches online in the WHO Database (Vigisearch); Erik Swahn demonstrated Vigimine and talked about the possibilities of this new tool being 'incorporated' in the existing Vigisearch system. William Frempong outlined the facilities available at *the* UMC for providing literature support to participants.

Ed Napke (the longest-serving reviewer) chaired a full discussion on a variety of topics of concern to the reviewers:

- Rechallenge combinations for follow-up?
- Quality of reports
- Pharmacist, nurse and consumer reporting
- Examining reports prior to a signal
- Advocacy in pharmacovigilance
- Output format to reviewers
- Assessments from reviewers – preferred format
- Data sources for concomitant drugs
- Collaborations with National Centres, UMC, industry, and between panel members
- Improving communication among the signal review panel
- Publication of signals in scientific journals and beyond.

### Outcomes

The low quality of some reports in the WHO database is a problem although the BCPNN is not dependent on good quality of reports to be able to highlight associations standing out from the background of the database. Nevertheless, having to drop a signal because the cases are too poorly documented to be assessed is frustrating for reviewers. *the* UMC will continue to promote better quality reporting and will forward this message to the National Centres. Reviewers indicated their clear desire to work more closely with national centres and the importance of the public health impact of signals in precedence to early warnings.

The group referred to various issues caused by different international (but not global) harmonization processes going on outwith the WHO Programme. The ICH E2b November 2005 deadline was causing trepidation for many in the drug safety world, because of the regulatory need for some parties to comply with this standard and for which many had limited resources to implement.

The use of birth registries was discussed and it was agreed it would be taken forward. The panel also believed that publication of signals in scientific journals would help reach a much larger audience and this should be investigated.

Re-signalling was also a hot topic, the WHO Drug Information journal being one possible channel for strong signals. In addition, the WHO Pharmaceutical Newsletter might be used with continuing known problems.

The group felt that more regular meetings for signal reviewers were essential to improve their effectiveness.

Closing the meeting, Ralph Edwards summed-up by describing some new challenges, including medication error, lack of effect of medicines, sub-standard and counterfeit drugs, plus opportunities in the form of advising WHO on specific safety issues, public health programmes, and the WHO essential drugs programme.

Before a farewell drink at *the* UMC offices the group had one more social event – a guided tour at the Gustavianum museum. Erected in the 1620s to be the main building of Scandinavia's oldest university, it is now home to the Uppsala University Museum, and contains five permanent exhibitions including the Anatomical Theatre with an exhibit on early anatomical and medical studies and unique objects such as Celsius' thermometer.

### Participants:

- |                                  |                             |
|----------------------------------|-----------------------------|
| Ariel Arias, Canada              | Per-Olov Lundberg, Sweden   |
| Joanne Barnes, UK                | Ronald Meyboom, Netherlands |
| Jan Bruhn, Sweden                | Ed Napke, Canada            |
| David Clark, New Zealand         | Ana Maria Nunes, Portugal   |
| Anita Conforti, Italy            | David Ofori-Adjei, Ghana    |
| Andrew Czeizel, Hungary          | Alain Rohan, USA            |
| Peter De Smet, Netherlands       | Emilio Sanz, Spain          |
| Kenneth Hartigan-Go, Philippines | Ruth Savage, New Zealand    |
| Lorna Hazel, UK                  | Saad Shakir, UK             |
| Richard Hill, Australia          | Debbie Shaw, UK             |
| Sylvia Kardaun, Netherlands      | Krishan Singhal, India      |
| Milan Kriska, Slovakia           | Myles Stephens, UK          |
| Alice Kuruvilla, India           | Mary Couper, WHO            |

# Launch of Viewpoint Part 2

The inside story of international pharmacovigilance for the general and specialist reader

Publication of Viewpoint Part 2 completes the picture



It could be a useful resource for medical, nursing or pharmacy training, and may help staff in national ADR centres who want a quick summary of the international picture and of *the UMC's* work.

It's been a long time a-coming, but *the UMC* is proud to report that Viewpoint Part 2 is now available, joining its popular companion volume published in 2002.

Viewpoint Part 1 has been greeted with enthusiasm in many quarters as the first attempt to explain pharmacovigilance to a wide, general audience. The first edition of Part 1 is now out-of-stock and a revised version has just been reprinted.

Part 2 is much longer – 68 pages – and covers the headline issues in drug safety as well as the detail and the small print of the WHO Programme, the activities of *the UMC*, and the business of international pharmacovigilance. If you want a thorough – and accessible – description of the WHO Drug Dictionary or the meaning of neural networks; or an outline of issues about information for patients or medical error; signal detection or causality assessment; risk management or herbals – or dozens of other topics, then Viewpoint Part 2 is for you!

## Reaching out to professionals and non-specialists

Travelling around the world, *UMC* staff are often asked: 'What exactly does *the UMC* do?' It's not an easy question to answer in three sentences – now, here's the comprehensive answer in sixty-eight pages.

While much of Part 2 deals with scientific and technical matters, it is written and presented in a way that should make it attractive and accessible to an audience well beyond professionals and specialists. It's produced in full colour, with lots of photographs, diagrams and tables – designed to make the pages more manageable and the information more immediate.



It's hoped that Viewpoint Part 2 will find a wide audience to spread the important messages of drug safety to patients, students, the media and many more. It could be a useful resource for medical, nursing or pharmacy training, and may help staff in national ADR centres who want a quick summary of the international picture and of *the* UMC's work.



### Spreading it about

*the* UMC is keen that the substantial investment in the publication should be maximised by reaching the widest possible audience. Readers of Uppsala Reports are invited to suggest productive uses for Viewpoint and people or organisations to whom it should be sent – please contact [cecilia.biriell@who-umc.org](mailto:cecilia.biriell@who-umc.org) with any ideas. If you'd like further copies of Part 1 or Part 2, please contact Cecilia Biriell for those also.

Please do let the team know your views about the publication – you'll find an easy to complete comment form at [www.who-umc.org](http://www.who-umc.org) > publications. Reader feedback is really important, so please do take a few minutes to respond!

## Contents of Viewpoint Part 2

### The WHO Programme for International Drug Monitoring

1. Primary activities and membership
2. The Heart of the Programme:  
ADR reporting systems and signal detection
3. Products and services
4. Publications
5. Collaborations
6. Communications
7. Audiences
8. Training
9. Key terms and issues in pharmacovigilance
10. The current state of play
11. The role of *the* UMC

### Appendixes provide lots more detailed reference information:

1. The guardians of drug safety. Macro-environment of drug regulation
2. Acronyms
3. Definitions and glossary
4. Joining the WHO Programme for International Drug Monitoring
5. Current member and associate member countries of the WHO Programme
6. Caveat document
7. Bibliography of key UMC publications in scientific journals
8. The Erice Declaration
9. BCPNN: additional technical information
10. *the* UMC's signal detection process – Guidelines for reviewers

Viewpoint Part 1 has been welcomed in many parts of the world as an effective presentation of pharmacovigilance for lay audiences. Its an ideal way to spread drug safety knowledge beyond the professional boundaries, not least to editors and journalists



*Dr Patricia Vella-Bonnano, CEO Maltese Medicines Agency, Dr Natasha Azzopardi Muscat, Director EU and International Affairs, Ministry of Health, Malta, Mr Damien Bishop, Project Co-ordinator, MHRA and Dr Joan Gilvarry, Director of Human Medicines, IMB.*



*Niamh Arthur, Pharmacovigilance Co-ordinator, Irish Medicines Board*

## Twinning Project between Ireland, the UK and Malta

### *A report from Niamh Arthur*

In September 2004, Malta fulfilled the requirements to become the 75th full member of the WHO International Drug Monitoring programme. Malta is a small island in the Mediterranean Sea between Sicily and Tunisia, with a population of some 400,000 inhabitants, many of whom are bilingual, speaking both their native Maltese and English. As part of an EU Commission supported twinning project, the Irish Medicines Board (IMB) and Medicines and Healthcare products Regulatory Agency (MHRA) worked with the developing Maltese medicines agency, to establish their regulatory system, with the IMB responsible for training in the area of pharmacovigilance.

EU-funded Twinning Projects aim to develop modern and efficient administrations in accession countries that can implement the Union's legislation to the same standards as existing Member States.

The Twinning Project, between the IMB, MHRA and the Medicines Authority in Malta, provided the arrangement for the Maltese government to work with their Irish and British counterparts. The project, which began fourteen months before accession, in February 2003, finished recently in October 2004. Throughout this period, a member of the IMB staff, Ms Anne Gray worked at the Maltese medicines agency on a full-time basis, as Pre-Accession Adviser, co-ordinating all aspects of the twinning project.

The wider objective of this project was to support the establishment of a competent regulatory authority in Malta, known as the Medicines Authority.

### **The twinning programme**

A Twinning Covenant was agreed, which set out the targets and objectives in separate areas, each distinctly reflecting the organisation and systems required to regulate medicines and management of those systems. The implementation of appropriate processes for pharmacovigilance was one of the main priority areas in the project with Ms Niamh Arthur as the Key Result Area Leader. The objectives to be met or indicators of achievements in this area were:

- Establishing a structure and working methods for the pharmacovigilance unit and helping to enhance the skills of assessors
- Developing systems to facilitate monitoring of compliance on the part of industry, introduce and increase Adverse Drug Reaction (ADR) reporting by Healthcare Professionals (HCPs)

- Develop processing and monitoring techniques
- Examine ways of disseminating pharmacovigilance information more widely, particularly in the development of guidance notes etc
- Review of EU and WHO pharmacovigilance networks, including IT links.

### **Summary of twinning activities**

In the pharmacovigilance area Irish experts visited the Medicines Authority and worked with the Maltese staff in their own environment. This provided an opportunity for the twinning partners to see the local arrangements in place and also allowed training to be provided to a wider group of staff. IMB pharmacovigilance staff visited Malta eight times during the 20 month project timeframe, delivered a total of 58 days training to their colleagues in the Medicines Authority. Staff from the Medicines Authority also visited the IMB, which provided an opportunity to reinforce the training provided, allowed staff to see the IMB's working arrangements at first hand and to work on some practical pharmacovigilance issues.

During one of the pharmacovigilance twinning visits in May 2004, the national Maltese ADR reporting system was launched, at a lively interactive session attended by HCPs and the pharmaceutical industry. This included provision of guidance to HCPs and industry on national reporting requirements, with promotion of the national ADR system seen as a priority for the Medicines Authority. During subsequent twinning visits, visiting experts joined forces with staff of the Medicines Authority by participating in ADR seminars at the main hospitals in the Maltese islands, to raise awareness of the ADR systems and to encourage HCPs to report.

As outlined above, Malta has received the requisite number of ADR reports to qualify for full membership of the WHO International Drug Monitoring programme and actively participated in the 27th Annual National Centres Meeting in Dublin.

Undoubtedly, the collaboration and close ties that have been forged through twinning will be of long-term benefit to Malta. However, it has to be said that this exercise wasn't a one-way street, as many lessons were learnt from our smallest EU Member State throughout the twinning process.

# South–North collaboration for AEFI monitoring and pharmacovigilance

by Alex Dodoo (Ghana) and Jeremy Labadie (Netherlands)

The enormous challenges encountered when carrying out rigorous scientific research in resource-limited environments are not insurmountable. A recently-concluded study involving the Dutch and Ghanaian National Pharmacovigilance Centres shows that both developed and developing countries may gain by collaborating in research conducted in developing countries.

## Forming alliances

Following alliances formed during the Annual National Pharmacovigilance Centres Meetings in Tunis (2000) and Dunedin (2001) and also at the biennial UMC training course in Uppsala (2001), Ghana and The Netherlands decided to collaborate in research on adverse events following immunization (AEFI). A perfect opportunity was provided when, in 2002, Ghana decided to include hepatitis B and haemophilus influenzae type B immunization in the routine vaccination programme. This involved replacement of the existing DPT (Diphtheria, Pertussis, Tetanus) vaccine with a pentavalent vaccine – DTP+HepB+Hib. What is the safety profile of the pentavalent vaccine compared with the trivalent vaccine and how can this be assessed bearing in mind the paucity (or near absence) of data on AEFI in Ghana?

## Project implementation

To answer these questions a project entitled Safety monitoring of a new pentavalent vaccine (DTP+HepB+Hib) in Ghana's Expanded Programme on Immunization was initiated in July 2003. There was close collaboration between the Dutch and Ghanaian teams in the project design and implementation including development of data collection instruments and data analysis. A visit by the vaccine expert of the Netherlands Pharmacovigilance Centre Lareb (Jerry Labadie MD) at the pilot testing stage ensured avoidance of obvious pitfalls and utilisation of locally appropriate mechanisms to ensure collection of scientifically valid data. A subsequent visit midway through the project by two other Lareb experts (Dr Kees van Grootheest and Dr Eugene van Puijenbroek) provided the necessary monitoring, evaluation and mid-term assessment of the project. Preliminary assessment of the data assures the safety of the pentavalent vaccine in Ghanaians and provides useful baseline data on AEFI in the country.

## Overcoming problems

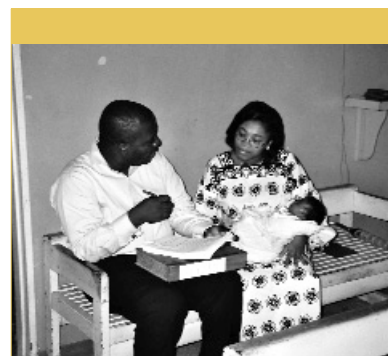
The challenges that confronted the project were many and included the lack of appropriate baseline data, meaning that the original hypothesis-driven comparative study had to be changed to a purely descriptive one. Relocation of participants to other geographical areas, preference to undertake vaccination closer to home and withdrawal of informed consent by some fathers after mothers (who attend the clinics) had consented to take part in the project were initial problems. These were overcome by increasing the number of study sites to include two polyclinics and a community immunization centre and also enhancing communication with patients to ensure that the non-interventional nature of the study was reinforced to the mothers (so that they can explain it to the fathers).

## Vaccines safety committee set up

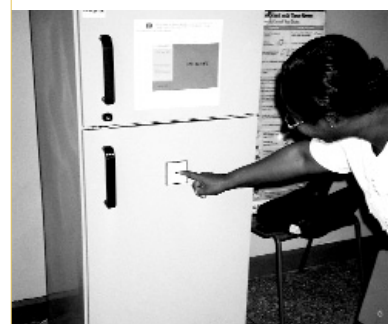
Spin-offs from this research include the sharing of research skills and expertise, exchange visits and exposure to health care practices in both countries. The study, which was funded by the Ghana-Dutch Partnership for Health Research and Development, also led to the establishment of a National Advisory Committee on Vaccine Safety to provide advice and direction on vaccine safety issues within the Ghana Health Service.

## Future work

Further research in this and other areas are planned under the on-going Ghana-Dutch Partnership for Health Development and Research – a truly South-North collaboration wherein a unique funding arrangement gives developing countries the drive to set the research agenda calling on developed countries' expertise when needed, relevant and in line with the resource-limited country's research and development agenda.



Interview of a participant.



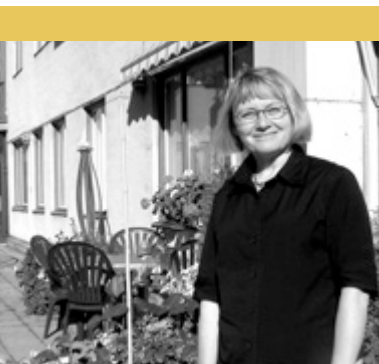
Refrigerator with outside temperature monitoring according to 'cold chain' storage procedures guidelines for vaccines.



Flowchart posted at several places in the hospital to help staff give care for study participants according to protocol.



Vaccines ready for use maintaining "cold chain" storage guidelines for vaccines.



Renan Bonnel, of the FDA, on the UMC terrace in September 2004

## FDA visitor in Uppsala

During September 2004, *the* UMC had the pleasure of an extended visit by Dr Renan A Bonnel, of the USA Food and Drug Administration, Office of Drug Safety. Renan has written her own account of her stay in Sweden.

"In September 2004, I had a professional development /training opportunity under the Food and Drug Administration's professional development program to visit the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden.

During my five-week visit, I observed, collaborated and shared information and perspectives, and worked side-by-side with drug safety scientists at *the* UMC in ongoing projects in the field of drug safety and pharmacovigilance.

The scope of my visit principally involved:

- 1) organization of *the* UMC and discussing practical experiences,
- 2) structure and research use of the WHO database (Vigibase),
- 3) signal detection and analysis, utilizing Bayesian Confidence Propagation Neural Network (BCPNN) method,
- 4) comparison of *the* UMC's BCPNN for ADR signal generation and the FDA's Empirical Bayes Geometric Mean method (EBGM), and
- 5) communication of safety information and UMC publications.

Vigibase, the World Health Organization database of adverse events, is somewhat similar to FDA's AERS database where ~200,000 reports annually are entered and the cumulative database has over 3 million suspected adverse event case reports. During my visit, I was introduced to a new interactive web application (Vigibase Online) where practitioners can send direct and timely reports. I was encouraged by this web-based reporting process between the practitioners and relevant destinations such as WHO, EMEA, FDA etc to receive direct and timely reports. This seems to offer an active surveillance system that may help to minimize the global dilemma of under-reporting of adverse drug reactions.

The signal detection and analysis team including Monica Plöen, Kristina Star, and Johanna Strandell introduced me to Vigibase, UMC's signal detection and validation methods. We were able to compare and contrast methods and learned from each other's experience and expertise. *the* UMC's Medical Advisor, Ronald Meyboom and I collaborated on a signal of interest and jointly worked to characterize the signal.

One of my interests as a safety reviewer is to determine how data-mining tools can both complement and enhance current safety evaluator pharmacovigilance practices. While I was in Uppsala, I learned about the everyday use of *the* UMC's Bayesian Confidence Propagation Neural Network (BCPNN) signal detection tool. Andrew Bate provided further insight into my understanding of data-mining as a safety evaluator tool and enhanced my knowledge. BCPNN method provides a quantitative measure of the strength of association of drug/reaction combinations in the database. As we currently pilot the data-mining tool using the EBGM method in FDA's Adverse Event Reporting System database, hands-on experience with the BCPNN helped me interpret possible differences using EBGM and BCPNN tools. Both methods are available as a tool for finding new adverse drug reactions in the WHO database.

I was also interested in learning about the preparation of UMC's publications, such as WHO Pharmaceutical Newsletter and Uppsala Reports that provide an easy-to-read account of news about global pharmacovigilance and drug safety. I appreciated Anna Kiuru's expertise and knowledge for the preparation of SIGNAL document.

We live in an increasingly global regulatory and information-laden environment where the analysis of drug safety information from many different countries can be of great benefit to the public health. My visit to UMC was a professionally rewarding experience and I enjoyed working with a kind, generous, competent and professional staff who deeply cared and believed about their work and contributions to drug safety."

*Marie Lindquist adds "we were delighted to welcome Renan and much stimulated by sharing the practical experiences of *the* UMC and WHO Programme with her, and look forward to further collaboration with FDA in the future".*



## Looking back and forward

Among the photographs kindly supplied by Professor Bill Inman to accompany the profile of him in Uppsala Reports 27 was one which required a long caption and some background to explain its context. The photograph shows a group which assembled in Honolulu in January 1977 – forty-two participants from eighteen countries in four continents – some experienced and others at the start of their careers in drug safety.

The 'International Workshop', sponsored by Ciba-Geigy and held in Honolulu, Hawaii from 24–28 January 1977, came in the aftermath of the practolol (Eraldin) scares. The way these serious problems arose had exposed the shortcomings of spontaneous adverse drug reaction (ADR) reporting systems, and the need to have ADR data which included a numerator and denominator. The co-chairs Frank Gross and Bill Inman commented: "We believe, with David Finney, that the concept of event-monitoring, rather than mere recording of suspicions that events may be drug-related, is the best strategy, not because he was the first to propose it nearly fifteen years ago, but because we believe he was right."

The symposium helped to consolidate, or initiate, systems in New Zealand (Intensive Medicines Monitoring Programme) and UK (prescription event monitoring) which sought to go beyond spontaneous ADR reporting.

The presentations and frank discussions at the meeting are recorded in the book 'Drug Monitoring' published shortly afterwards by Academic Press\*, which opens with the words "Another meeting on drug monitoring – was it necessary? Whom did it serve? Did it have any impact on the detection of adverse reactions, or did it even improve drug safety?" (words which could have been written about other subsequent pharmacovigilance meetings).

Despite the programmes mentioned above, and for a variety of reasons, some of the proposals and recommendations were not developed further, and there is still some way to go before event-monitoring is widely implemented.

The contemporary relevance of the Honolulu symposium is manifest in the recent WHO Programme meeting in Dublin which demonstrated the renewed concern about complementary methods of pharmacovigilance, besides spontaneous reporting. We hope that the 2004 discussions on focussed surveillance methods may also bear fruit as did the 1977 meeting, and send our good wishes to all those who took part.

\*Gross FH, Inman WHW, eds. *Drug Monitoring. Proceedings of an International Workshop held in Honolulu from 24 to 28 January 1977.* London, Academic Press, 1977.



**Standing** K R Hammond, *University of Colorado, USA.* K Carter, *Syntex Corporation, USA.* A N Walker, *Ciba-Geigy (Hong Kong) Ltd, Hong Kong.*

A Harrestrup-Andersen, *St Lukas Stiftelsen, Denmark.* J F Dunne, *WHO.* E Napke, *Health and Welfare, Canada.* P Sartwell, *USA.* B Berde, *Sandoz Ltd, Switzerland.* D J Finney, *University of Edinburgh, Scotland.* J M Crawford, *Department of Health, Australia.* F H Gross, *Pharmakologisches Institut der Universität, Heidelberg, Germany.* D Sackett, *McMaster University, Canada.* A Liljestrand, *National Board of Health and Welfare, Sweden.* J Koch-Weser, *Merrell International, France.* O de S Pinto, *Ciba-Geigy Ltd, Switzerland.* D H Lawson, *Glasgow Royal Infirmary, Scotland.* Idänpään-Heikkilä, *National Board of Health, Finland.* H Kewitz, *Freie Universität Berlin, Germany.* G F Jgraff, *Bundesgesundheitsamtes, Germany.* Y Yoshitoshi, *Hamamatsu University, Japan.* R Kobi, *Ciba-Geigy Ltd, Switzerland.* H Studer, *Medizinische Universitätsklinik Bern, Switzerland.* S Lock, *BMJ.* M Gent, *McMaster University, Canada.* W F Whimster, *Technical editor.* V W M Drury, *England.* J G Domenet, *Geigy Pharmaceuticals, England.* I Darmansjah, *University of Indonesia.* R Temple, *FDA, USA.* R A Ellis, *Ciba-Geigy Corporation, USA.* S Shapiro, *Boston University Medical Center, USA.* Y Aso, *Chiba University, Japan.*

**Sitting** H Jesdinsky, *Institut für med Statistik und Biomethematik Dusseldorf, Germany.* C R B Joyce, *Ciba-Geigy Ltd, Switzerland.* G Davey, *England.*

A Escher, *Ciba-Geigy Ltd, Switzerland.* W H W Inman, *Committee on Safety of Medicines, England.* W M Wardell, *University of Rochester, USA.* N Shimizu, *Teikyo University School of Medicine, Japan.* S Chanai, *Japan.* R H B Meyboom, *Netherlands Centre for Monitoring of ADRs.* K Siehr, *Max-Planck Institut, Germany.* J Gelzer, *Ciba-Geigy Ltd, Switzerland.* E G McQueen, *Committee on Adverse Drug Reactions, New Zealand.* D C G Skegg, *University of Oxford, England.* C Anello, *FDA, USA.*

Igor Francetic writes:

## 30th anniversary of Croatian national centre

### Origins in Yugoslavia

Our story started back in 1974 when the Ministry of Health of the former Yugoslavia was accepted as the 18th country in the WHO Programme for International Drug Monitoring. From the beginning the Drug Centre in Zagreb (now capital of Croatia) was nominated National Centre for ADR monitoring for the whole country. The operational unit of the national centre was in the Division of Clinical Pharmacology, Head of the Division at that time being Professor Bozidar Vrhovac. As first official contact and initiation of the activities of national centre, Professor Jan Venulet from WHO Headquarters came to Zagreb. The meeting of the Director of the Drug Centre Dr Savo Zlatic, Head of Division of Clinical Pharmacology, Professor Vrhovac and Dr Francetic – collaborator to Professor Vrhovac, and Professor Venulet from WHO can be regarded as official start and functioning of National Centre for ADR monitoring within the WHO Programme.

Most of the activities were in Zagreb and around 80% of the ADR reports came from the neighbourhood. Lots of effort was put into widening the reporting throughout the country and numerous lectures and seminars were given.

### Memorable WHO meetings hosts

Active participation of our national centre culminated in 1985 when the WHO Annual Meeting of representatives of National Centres took place in Dubrovnik. According to the recollections of participants this was one of the most memorable meetings – both for scientific and social content!



*Dubrovnik (Stradun), 1985; from left: Liv Kjeldas (Norway), Ralph Edwards, Bozidar Vrhovac, Igor Francetic, Neda Vocanec, John McEwen (Australia).*

### Croatian national centre born

In 1991 Croatia became an independent state and the centre in Zagreb became the Croatian National Centre for ADRs within the WHO Programme. Since the Drug Centre ceased to exist, the Croatian national centre at the Division of Clinical Pharmacology, Department of Medicine in University Hospital Centre, resumed its work, according to the official recognition by Ministry of Health of Croatia. As the Croatian national centre was operating in a university hospital, we had the opportunity (which we took) to implement teaching and training for numerous students, interns, residents and postgraduates in different aspects of ADRs. Currently we have regular lectures at postgraduate level in clinical pharmacology, seminars for the 4th year students of medicine, and lectures for residents and fellows in the hospital.

As with many other national centres we operate referring to our Ministry of Health and Welfare. An annual report is sent to Minister of Health and Welfare and published in 'Pharmaca' – our national journal devoted to drugs.

### Commitment and enthusiasm

On average we receive around 1,200-1,500 ADR reports per year from a population of 4.5 million. Despite the fact that we do not have permanently employed physicians in our centre, we manage to send a personalized letter to each and every reporting doctor or pharmacist. This is greatly valued by reporters, and most of them become permanent reporters and we have a negligible drop-out rate.

The present situation of national centre for ADR monitoring is rather difficult since a National Drug Agency has been founded and, officially, has to deal with ADR monitoring; but the Agency has neither logistics nor manpower to do this, and for unknown reasons seems to be reluctant to officially delegate this job to the National Centre.

Activities of Croatian National Centre were and are similar to other National centres co-operating with WHO. However, what is unique about our Centre is that from 1974 we have never had a budget and we still operate relying on long-lasting, contagious enthusiasm.

*Croatian journal – Pharmaca*

## UMC posters now on web

As well as providing key-note speakers and oral presenters, the Uppsala Monitoring Centre regularly has posters accepted for presentation at international meetings. These posters have covered all areas of research and study engaged in by the UMC, either independently or in collaboration with others.

We have now made available the following selection of posters in Adobe pdf format for viewing or downloading (the maximum size is 665 Kb).

- Bisphosphonates and Ocular side effects (Kiuru A, Fraunfelder F, Edwards IR)
- Selective Serotonin reuptake inhibitors (SSRIs) and blood pressure (Meyboom RHB, Pettersson M, Kiuru A)
- WHO Signals 1998-2001 A follow-up (Star K, Ståhl M, Strandell J, Pettersson M, Lindquist M)
- Impact of signals generated from the WHO database (Ståhl M)
- Pattern recognition using a recurrent neural network and its application to the WHO database (Bate A, Lindquist M, Orre R, Edwards IR)
- Automated evaluation of signals as group effects or drug specific using the WHO database (Bate A, Lindquist M, Edwards IR, Orre R)
- Pattern detection for celecoxib and rofecoxib in the WHO database (Bate A, Norén N, Orre R, Lindquist M, Edwards IR)
- International availability of translations of WHO and UMC pharmacovigilance texts (Bowring G, Olsson S)
- Vigimed, an international drug safety e-mail discussion group (Johansson K, Meyboom R)

You can check these out in the posters section of the Publications page of our website. Further posters will be added to the site during the coming year.

[www.who-umc.org](http://www.who-umc.org) > Publications

### The Statin Wars

Ron Meyboom and Ralph Edwards write

The on-going controversy over statins has been met by a considered response from Ron Meyboom, Medical Advisor at the UMC, and Ralph Edwards.

HMG-CoA reductase inhibitors were introduced around 20 years ago, to lower the risk of cardiovascular and cerebrovascular morbidity. In the following years, more has become known about the serious adverse effects of statins and doubts have emerged with regard to their balance of benefit and harm. They mention 338 spontaneous reports of rhabdomyolysis or myopathy in the WHO ADR database associated with fatal outcome, and go on to discuss the manner in which new drugs are introduced to public use and current limitations in post-marketing surveillance.

The full comment article can be found at Meyboom RHB, Edwards IR. Rosuvastatin and the statin wars – the way to peace. *Lancet* 2004; 364:1998-99.

### WHO Signals – 1998 to 2001 A follow-up

K Star, M Ståhl, J Strandell, M Pettersson, M Lindquist

**INTRODUCTION**

Continuing improvements in safety within the work of signal detection and analysis at the Uppsala Monitoring Centre (UMC), Norway (NOR), and the Uppsala Monitoring Centre (UMC), Sweden (SWE), have led to the introduction of the Periodic Confidence Interval Signal Search (PCISS) in 1998, the effectiveness of which has previously been demonstrated, and the introduction of a new system in 2001, which is a filtering process to narrow down the number of candidates for review and to focus on areas of greatest importance. The WHO signals in this study were mainly highlighted by the PCISS, and around 80% of them had not been previously reported in the official safety surveillance systems. This study will be the first to make follow-up of WHO signals that will be implemented in the UMC, in order to further improve signal detection efficiency.

**AIM**

To describe the occurrence of drug adverse drug reactions (ADR) combinations included in the 1998 to 2001 issues of 'Signal' in the drug reference sources from 2001.

**METHOD**

Drug-ADR combinations, included in the national surveillance systems 'Signal' from 1998 to 2001, were followed up and checked for occurrence in the Periodic Confidence Interval Search (PCISS), 'DrugNet', and the Summary of Product Characteristics (SPC) for the United Kingdom between July and October 2001. The PCISS was used to check the status of the combination in the issue of the signal.

The findings were classified using the following system: Y: the status matches or a more specific term was classified for the drug; X: a higher level term was classified for the drug, or the same reaction as the main specific term was classified for another drug in the same group or which the drug was not selected; N: the reaction was not classified for the drug in the drug group; NA: the drug was not included in the reference source.

In part of the analysis, combinations were selected by using the PCISS measure of disproportionality called the Information Component (IC). The IC<sub>025</sub> was calculated over time and the lower 95% confidence limit (IC<sub>025L</sub>) is positive, the likelihood of a positive association between the drug and the ADR is high.

**RESULTS**

A total of 284 drug-ADR combinations were included in 124 different signal headings in 14 issues of 'Signal' from 1998 to 2001.

**DISCUSSION**

Seven percent (60%) of all signal combinations from 1998 to 2001 had a positive trend in the time of the source where reported in 2001, and 10% had a positive trend in one or more sources.

It is mainly reactions concerning 40% of the combinations found in the PCISS that were classified as 'Signal' over a 3-year period. The WHO reference is a signal should be 'highlighted as non-specific, documented previously'. It is suggested that routine screening of drug reference sources before the signal is published, which is part of the signal system, will reduce the proportion. Nevertheless, the UMC will occasionally screen an extensive number of signalling drugs as being listed in the PCISS, since the PCISS includes not only national ADRs, but also adverse events and generally covers more reactions than the reference information sources used in this study.

A signal is a hypothesis that is often based on limited case information. There is a default balance between being too sensitive and being too specific. Thus, to make a signal to stand the test, and therefore likely to be suitable and not the outcome of the combination of the hypothesis. To maintain a certain level of sensitivity, one must allow for the possibility that 'false' signals will arise and that there will be a corresponding need to monitor and verify such signals before they are accepted as established 'signals'. Thus, on the one hand, of course, to have a limited number of 'false' signals.

The combinations not listed in the reference sources are however not necessarily 'false' signals. A period of time is necessary to see if the signal is true or not. It is possible that a signal that is initially thought to be a false signal may turn out to be a true signal after a longer period of time. It is therefore suggested that a signal that is initially thought to be a false signal may turn out to be a true signal after a longer period of time. It is therefore suggested that a signal that is initially thought to be a false signal may turn out to be a true signal after a longer period of time.

**CONCLUSION**

A majority of the signal combinations in this study could be found in at least one of the drug reference sources in 2001. Seven of the signal combinations were newly identified in the PCISS in the issue of the signal but it is expected that routine screening of drug reference sources before the signal is published, which is part of the signal system, will reduce the number. Some of the signals were found in 2001 even before the 2001 ADR surveillance system, which may suggest more are being transferred in the drug group. This study has been part of the implementation of a routine follow-up process of signals and will provide a base for the evaluation of the signal system and thereby further improve the WHO signal process.

**ACKNOWLEDGEMENTS**

The authors are indebted to the national centers and the UMC signal review panel for their contributions. The operating and maintenance, however, are not necessarily those of the various centers over the 12993.

Star K, Ståhl M, Strandell J, Pettersson M, Lindquist M. WHO Signals – 1998 to 2001. A follow-up. *Pharmacoepidemiol Ther* 2004; 28: 1998-99.

## Pharmacovigilance in Portuguese and French

### Farmacovigilância em Portugal

520 pages soft cover with CD ROM  
ISBN 972-8425-48-1  
Published by INFARMED – Instituto Nacional da Farmácia e do Medicamento, Ministério da Saúde  
A comprehensive account in Portuguese of the administrative and scientific basis of the pharmacovigilance system in Portugal.

### Bonnes Pratiques de Pharmacovigilance

30 pages soft cover Published by the Centre Anti Poison et de Pharmacovigilance du Maroc (www.sante.gov.ma)

A succinct handbook in French describing the Moroccan system of pharmacovigilance and "defining the roles of each person involved in the national pharmacovigilance system".

## WHO herbal safety guidelines

The WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems, mentioned in Uppsala Reports 27, is available from: Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland, e-mail [bookorders@who.int](mailto:bookorders@who.int).  
The 32-page main contents are:

- Introduction, Background; Objectives, Glossary
- Pharmacovigilance and the WHO International Drug Monitoring Programme
- Challenges in monitoring the safety of herbal medicines
- Safety monitoring of herbal medicines
- Communication
- References, bibliography

There are also five useful annexes and the complete text of 'Safety Monitoring of medicinal products: guidelines for setting up and running a pharmacovigilance centre'.

## Chinese periodicals

We have also received samples of the new Chinese Journal of Pharmacovigilance (in Chinese)

ISSN 1 672-8629

Further details are available from the website [www.cdr.gov.cn](http://www.cdr.gov.cn) or e-mail [ywj@cdr.gov.cn](mailto:ywj@cdr.gov.cn)

The National Center for ADR Monitoring, China is also publishing a 'Chinese Adverse Drug Reaction Information Bulletin' also available via the Chinese National Centre website as above, of by enquiring with e-mail [chinaadr@adr.gov.cn](mailto:chinaadr@adr.gov.cn)

## UMC publications in Chinese

'The Importance of Pharmacovigilance' and 'Dialogue in Pharmacovigilance' have been translated, organised by Dr Du Wenmin at the Shanghai Regional Centre for Adverse Reaction Monitoring, 532-50 Yu Yuan Road, Shanghai 200040, P.R.China, e-mail [duwenming@smda.gov.cn](mailto:duwenming@smda.gov.cn) The ISBN is 7-5428-3666-8

(see also article on China, page 7).



Farmacovigilância em Portugal



Chinese Journal of Pharmacovigilance and Chinese ADR Information Bulletin





*Medicines: using them safely*

## Popularising the drug safety message in Ghana

Pharmacist and author Bernard Appiah has done the people of Ghana a good service: his excellent short book, *Medicines: using them safely*, will help everyone who reads it deal with medicines more rationally and intelligently. It's written in an informal, approachable style, with lots of examples, straight from the shoulder advice, and a scattering of cartoons and drawings. It's a great model of how to get the drug safety message across to ordinary people and could be of benefit in many English-speaking countries.

## WHO booklet

WHO policy perspectives on medicines – Pharmacovigilance: ensuring the safe use of medicines. Produced by our colleagues at Quality and Safety, Medicines in Geneva, this booklet gives some basic facts about pharmacovigilance and activities of the WHO Programme.

It will soon be translated into all six official WHO languages, the first being the Russian version, followed by French and Spanish.



*Pharmacovigilance: ensuring the safe use of medicines*  
Available from [bookorders@who.int](mailto:bookorders@who.int)  
or phone +41 22 791 2476

## Visitors from the East

On 30 November 2004 the UMC was visited by Dr Lala Margaryants from Armenia and Dr Issupov Salomiddin from Tajikistan. This was the first time we had welcomed visitors from these countries. They were given an overview of the activities of the UMC and the support and services national pharmacovigilance centres can receive from the WHO Programme.

Armenia has been a member of the WHO Programme for International Drug Monitoring since 2001 (see Uppsala Reports 16, page 4 for a short report), while Tajikistan is presently considering establishing a national pharmacovigilance system. Among the many issues discussed was the need for guidelines and pharmacovigilance training in the Russian language.



*DrDr Salomiddin (standing) with Sten Olsson in the UMC offices, overlooking Stora Torget in Uppsala*



## Buying UMC services online

*the* UMC's Products and Services website is not only up and running, but it is now possible to make the majority of orders via the webshop. As well as placing your order in the webshop, you can also calculate the cost and, where appropriate, generate a standard licence agreement. In addition, we have started to develop user group areas so that customers will always have easy access to the information they need, on our website. Do explore [www.unc-products.com](http://www.unc-products.com), your partner in clinical trials or drug safety operations.

## Updates – 3rd Quarter 2004

The new versions of the computerised WHO Drug Dictionary (WHO-DD) and WHO Adverse Reaction Dictionary (WHO-ART), containing information for the 3rd quarter of 2004 are now available. These were sent to subscribers during October/November 2004. The WHO-DD pack contained the updated version of WHO-DD along with a wealth of background material.

## Need help?

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

You can e-mail:

[drugdictionary@unc-products.com](mailto:drugdictionary@unc-products.com) for comments about the WHO-DD, corrections and additions, and

[katarina.hansson@unc-products.com](mailto:katarina.hansson@unc-products.com) 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.

Data files for the 4th quarter of 2004 should be available during March 2005.

## New agreement

A new collaboration between the maintenance organisation of WHO-DD – *the* UMC – and IMS Health makes the dictionary even more comprehensive. The IMS data will be loaded into WHO-DD on a country-by-country basis, and each country will be kept up-to-date on a quarterly basis. Each country that is loaded will result in near complete coverage of the products on the market in that country. The incorporation of IMS data in the WHO-DD will lead to tens, or even hundreds of thousands of new entries.

However, by doing that we need to update our standard licence agreement with clauses related to our collaboration with IMS. On our website

customers can log on and get access both to the current WHO-DD licence agreement the new and updated WHO-DD licence agreement, as well as important background information and instructions. Each customer has received an e-mail with the necessary information about how to log on to our website. If you have any questions regarding this, don't hesitate to contact us through our website [www.unc-products.com](http://www.unc-products.com).

## New price list

The new price list valid from 1st of January 2005 is now available and has been distributed to our customers at the end of November 2004. The webshop has also been updated. If you are interested in obtaining your own copy, please tap into our website and download.

## Meet us there!

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

- 4th Annual Workshop for Contemporary Pharmacovigilance and Risk Management Strategies 24-27 January 2005, Washington, DC, USA.
- 17th Annual meeting, Euromeeting – Medicine in changing times - Booth 113 7-9 March 2005, Lisbon, Portugal
- 20th Annual Clinical Data Management Symposium 3-6 April 2005, Hyatt Regency Crystal City, Arlington, VA, USA

We look forward to seeing many of you at one of these; if you wish to arrange a meeting with us, please contact Mats Persson, e-mail [mats.persson@unc-products.com](mailto:mats.persson@unc-products.com)

## Have you moved?

If there is a mistake in our database, or you have changed your address, do let us know as soon as possible.

Please either log on to our web site [www.unc-products.com](http://www.unc-products.com) to correct your address, or e-mail your correct address to us. We will then be able to update our address lists. Thank you!



Get in touch with members of the Products and Services team for help or enquiries

# COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
10 February 2005	Pharmacovigilance (Introductory course)	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
10-11 February 2005	New Challenges in Clinical Safety, Pharmacovigilance and Vaccine vigilance	Barcelona, Spain	ISoP Administration Tel/Fax: +44 (0)20 8286 1888 www.isoponline.org
11 February 2005	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
24-25 Feb 2005	Adverse Event Reporting in Pharmacovigilance	London, UK	IIR Tel: +44 (0)20 7915 5055 www.iir-lifesciences.com
7-9 March 2005	DIA Euro meeting	Lisbon, Portugal	DIA Tel: +41 61 225 5151 E-mail: diaeurope@diaeurope.org www.diahome.org
15-16 March 2005	Pharmacovigilance Conference: ADR Monitoring and Safety Surveillance Strategies in Europe and the USA	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
13-14 April 2005	Back to Basics in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
21-22 April 2005	Adverse Event Reporting in Pharmacovigilance	London, UK	IIR Tel: +44 (0)20 7915 5055 www.iir-lifesciences.com
26-28 April 2005	9ème Congrès Annuel et 26èmes Journées de Pharmacovigilance	Bordeaux, France	Secretariat Tel : (33) 2 35 14 86 04 Fax : (33) 2 35 14 86 09 E-mail: secretariat@pharmacol-fr.org
23 May-3 June 2005	The 10th international training course 'Pharmacovigilance - The Study of Adverse Drug Reactions'	Uppsala, Sweden	the UMC Tel : +46 18 65 60 60 E-mail : info@who-umc.org www.who-umc.org
26-30 June 2005	DIA 41st Annual Meeting	Washington DC, USA	DIA Fax : +1 215 442 6199 www.diahome.org
6-7 July 2005	Risk Benefit Assessment in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
21-24 August 2005	The 21st International Conference on Pharmacoepidemiology Et Therapeutic Risk Management ISPE	Nashville Tennessee, USA	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
3-8 September 2005	International Pharmaceutical Federation Congress; pre-meeting on 'Information, Pharmacovigilance and Patient Safety'	Cairo, Egypt	FIP Congresses Et Conferences Tel:+31-(0)70-302 1982/1981 Fax:+31-(0)70-302 1998/1999 E-mail: congress@fip.org www.fip.org
17-19 October 2005	ISoP Annual Scientific Meeting	Manila, the Philippines	ISoP Administration Tel/Fax: +44 (0)20 8286 1888 www.isoponline.org



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