

# MUR54



**Caveat document | China | Training course**

**Paediatric safety | Pictograms | Access to data**



Marie Lindquist  
Director  
the Uppsala Monitoring  
Centre

*One of my colleagues, a very thoughtful person, said to me not long ago that she was worried that we don't do enough for patients. We all talk about pharmacovigilance starting and ending with patients, and patient safety being our foremost concern – but are patients really helped by what we do today?*

*It is true that our concentration in the UMC has been on developing data collection and analysis methods and tools for WHO Programme members and for our own signal analysis work, alongside the continuous development of the drug dictionaries which are used by hundreds of pharmaceutical companies, clinical research organizations and others world-wide.*

*We think and hope that the result of our work will benefit patients. What we and many others do to develop pharmacovigilance systems and advanced signal detection methods is important. But is there not a real risk that we are so distant from the clinical setting that we shall never find out what impact, if any, our efforts have for patients and health professionals in their daily lives?*

*It has been said that 'statistics are patients without tears'. Does the fact that many of us pharmacovigilantes refer to patients as 'end users' in itself indicate that we see patients as numbers and not persons? Well, you may argue, it is easy for her to sit in her comfortable office (actually, I am sitting on a not-too-comfortable old chair in my study at home) and talk about getting close to patients – we are already drowning in work, trying to do our job.*

*I am not arguing to add a new burden to our busy lives, but to consider if we can use our imagination and creativity to reach what should be a tangible goal – a better dialogue between patients and health professionals and those of us who don't meet them on a daily basis. Most pharmacovigilance systems rely on old techniques: information being typed (or scribbled, more likely) onto paper forms and transferred into databases through more or less user-friendly interfaces. Would it not be better if we could capture the information in a less time-wasting and more attractive way? Why is it that*

*not every computerised patient record/prescription support system has a feature that allows the doctor to 'flag' a diagnosis as a possible adverse reaction, and by pressing a 'send' button, to automatically transfer the relevant data to the pharmacovigilance centre? Some do, but this should be universal: double data entry is one of my pet hates – it should never happen! If I were a doctor, I would be really irritated about the thought of filling out a form with much of the same data that I had just entered into the computer.*

*Direct reporting to national pharmacovigilance systems by patients has moved from something seen with a level of suspicion by many in pharmacovigilance, to a positive reality in some countries; it is now part of the legislative requirements in the European Union. We should think hard about what we can do to make patient reporting a real success. I am not talking about number of reports received, but a dynamic and truly interactive communication and learning process for all involved parties. Anyone heard of smartphones? Apps? I am convinced that the new techniques available today have opened up opportunities that we could only have dreamt of a few years ago – from giving useful information to patients, to aiding their interactions with health professionals, to sharing their good and bad medicines experiences with other patients and regulators. It seems to me that the rapidly growing global availability of smartphones will help us do this in many more places in the world. As always, my ambition is that we in the UMC should be in the frontline of development, and I am excited about the prospect of really bridging the gap between those who need, and provide, care, and us who should be there to help them. Can we improve our bedside manner? Back to the future!*

A handwritten signature in black ink that reads "Marie Lindquist". The signature is written in a cursive, flowing style.



**FEATURES**

**6**  
Caveat updated

**12-13**  
The participants make 2011 UMC course a huge success

**14-15**  
Fresh developments on assessing documentation grading

**17-18**  
UMC research work

**19**  
Memories of David Clark

**REGULARS**

**2**  
Director's Message

**4-5**  
News from the WHO Programme – access to VigiBase; China

**7**  
Challenges in new vaccines

**8-11**  
News from Around the World – Netherlands, Belarus, Thailand, Argentina, Iceland, South Africa

**16**  
An update from Monitoring Medicines

**20**  
Publications – articles on safety in children and a new pharmacovigilance book

**21-22**  
News from Bredgränd – visitors to the UMC office and new staff

**23**  
Courses and conferences



**Agreement with national centre in China**

Important collaboration between Chinese pharmacovigilance and the UMC



**UMC course 2011**

A lively and interactive, highly-successful international course in Uppsala



**Recent UMC research**

A look at some latest papers and research trends



**UMC staff activity**

Monitoring the fitness at the UMC



# Widening access to VigiBase data

Sten Olsson

At its latest meeting in April 2011 the WHO Advisory Committee on the Safety of Medicinal Products (ACSoMP) discussed the issue of making data in VigiBase more widely accessible<sup>1</sup>. It was noted that many stakeholders outside of national pharmacovigilance centres have legitimate reasons to access data from the international repository. There is a growing demand for transparency of patient safety data in society and such demands have been directed to WHO from many different groups, including representatives of academia, professional and general media, patients and the public. Recommendations from the International Conference of Drug Regulatory Authorities (ICDRA) have also advocated greater openness to data in the WHO database. Case reports of suspected drug-related problems, excluding details

with the potential of identifying individuals, are considered public information in many countries and several countries have devised web-based search tools for public use. Being aware of the unconfirmed and sensitive nature of data stored in VigiBase ACSoMP members were mindful of the fact that data have to be made available to a wider audience in a responsible manner, with relevant caveats, to avoid misinterpretation.

UMC is currently in the process of applying new strategies to ad hoc analyses of data in VigiBase and will offer more advanced tools to national centres in this regard. ACSoMP recommended the UMC in this context to also devise a search facility for use by the public. Experiences from similar services in national databases should be taken into account in this process. It was agreed that

suggested data compilation models be distributed to national pharmacovigilance centres for consultation before the implementation. UMC representatives estimated that a first public search facility for VigiBase might be made available during 2012. UMC was also recommended to extend VigiBase-related statistics available from the UMC website to include e.g. reporting statistics by year and by country.

In a previous recommendation ACSoMP requested evaluated signals from the WHO/UMC signal analysis routine be published in the *WHO Pharmaceuticals Newsletter* but only after due circulation to national pharmacovigilance centres.

1. [www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/recommendations.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/recommendations.pdf)

# Training opportunity in West Africa

Effective Communications in Pharmacovigilance is a 3-day course to take place in Accra, Ghana for people working in any aspect of pharmacovigilance and patient safety – in pharmacovigilance centres, hospitals, community settings, public health programmes, industry and academia.

Running from 11-13 October, it will cover everything from patient information to crisis management, from risk communication to media relations, from ADR forms to teaching methods – a one-stop shop for vital communications knowledge and skills to make pharmacovigilance work better.

Full details of the costs, accommodation, and an application form are available on [www.who-umc.org](http://www.who-umc.org) (Go to Pharmacovigilance – Education & Training) or by contacting Richard Nyamah at UMC-A: [kwaci@hotmail.com](mailto:kwaci@hotmail.com) or [info@pvafrica.org](mailto:info@pvafrica.org).

The course will be led by Bruce Hugman, UMC's communications specialist. The course numbers are limited, so hurry if you'd like to participate!

The course group will contain no more than 35 participants.

The course will include:

- The characteristics of effective communications
- Communications challenges in pharmacovigilance and patient safety, and how to address them
- Communicating risk, risk and benefit and uncertainty
- Effective communication with healthcare professionals and patients
- Effective systems for ADR reporting, including design of forms and materials
- The principles and skills of effective teaching and training
- Media and public relations
- Managing meetings
- Crisis management and communications.

# WHO Programme news

## India

WHO Geneva has been informed that the central organization of the Pharmacovigilance Programme of India (PvPI) for monitoring adverse drug reactions is to be moved. Most recently it has been based at the All India Institute for Medical Sciences in Delhi, the major clinical and research centre in India. From April this year the functions have been transferred to the Indian Pharmacopoeia Commission (IPC) in Ghaziabad, Uttar Pradesh. The IPC is an

autonomous institution of the Ministry of Health, whose function is to set and regularly update standards for drugs commonly required for treatment of disease in India.

The new organization will continue to use VigiFlow™ for transmission of reports to the WHO database; an agreement has been signed in June. Already eleven established regional centres in India have been entering ICSRs, amounting to more than 9,000 within a few months.

## New Associates

Over the last quarter WHO has received expressions of interest from Liberia, Mauritius, Gambia, Cape Verde and Niger to join the WHO Programme for International Drug Monitoring. We look forward to further developments, and hopefully welcoming these countries soon when they fulfil the requirements to become full members of the Programme.

# UMC-SFDA collaborations formalized

Henrik Sahl

The Uppsala Monitoring Centre's vision is to improve worldwide patient safety – and one fifth of the world's population is living in China. This fact alone shows the importance of a new collaboration between UMC and the National Center of ADR Monitoring in China.

China has been a full member country of the WHO International Drug Monitoring Programme since 1998. With an increasing amount of ADR data in the Chinese national database it has become more and more difficult to find the resources for translating this data into English so that it can be transmitted to VigiBase™, the global ICSR database, currently containing over 6 million reports from around the world. This has created a need for UMC to be able to accept reports in the Chinese language.

The National Center of ADR Monitoring and UMC have had several exchanges of knowledge and visits in recent years. These have formed an excellent foundation for cooperation in areas such as technological communication and exchange, to harmonize the China Adverse Drug Reaction Monitoring data and VigiBase data. To achieve this we will embark on five projects that will run over approximately two years. This includes:

- Upgrading the current Chinese version of WHO-ART (adverse reaction terminology), which will make it possible to use the bridge between WHO-ART and MedDRA in the future
- Improvement of Drug Dictionary China (which has been developed by

UMC specifically for China). This can handle Chinese medicinal product names with Chinese characters either as a stand-alone coding system or by converting them into WHO Drug Dictionary Enhanced's global coding system

- Establishment of a data exchange platform, so that data can be transferred in a format accepted by the two different databases
- Standards for Chinese-English translations of terms and controlled vocabularies, and



At the ceremony (left to right): Marie Lindquist (UMC Director), Wu Guizhi, Du Xiaoxi (National Centre Director) and Zhang Cheng Xu (National Centre Deputy Director).



Du Xiaoxi and Marie Lindquist at the signing ceremony with staff from both organizations behind

- Establishment of co-operation within signal detection and data mining systems to advance ADR signal detection work procedures

The agreement was signed by UMC's Director Marie Lindquist and National Center of ADR Monitoring's Director Du Xiaoxi. The official signing ceremony was held in Beijing the 4<sup>th</sup> of July with a delegation from UMC visiting the National Center.

In a separate development, following previous similar events, a delegation of Chinese regional centre staff will come to Uppsala in October for a three-week pharmacovigilance training course organized by the UMC.

## Dubrovnik plans

Geoffrey Bowring

### Meeting invitation

Official letters have been received at pharmacovigilance agencies around the world, inviting countries participating in the WHO Programme to join together in the city of Dubrovnik, Croatia from 30 October – 2 November 2011 for the annual meeting of the WHO Programme for International Drug Monitoring.

The draft agenda and more information regarding the meeting will be sent to national centres and placed on the Collaboration Portal shortly. Information on

travel and accommodation will also be provided in due course by the UMC at the VigiMed section of the Collaboration Portal.

Pre-meeting tutorials and other courses take place on 30 October, with the main meeting from 31 October.

### Venue

The conference will be the 270-room Dubrovnik Palace Hotel, a 5\* hotel overlooking the Adriatic, within walking distance of the old centre of Dubrovnik.



# Caveat updated

Richard Hill

Data of the kind generated by spontaneous reporting in over one hundred countries requires considerable caution and skill in interpretation. Since 1992, the UMC has issued a 'Caveat document', a formal advisory warning clearly outlining the limits for data use and interpretation, which accompanies data extracted from the WHO

global ICSR database sent to third parties and is included in the Signal document.

Following discussion at WHO's Advisory Committee on the Safety of Medicinal Products (ACSoMP) meeting in Geneva on 31 March and 1 April, the WHO-UMC Caveat document has been updated. This was done

in order to better reflect the nature of the reports in VigiBase, for example, that many National Centres now accept reports directly from consumers. The new version of the Caveat also seeks to clarify UMC's role in the report collection process.

## CAVEAT DOCUMENT

### *Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring*

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

Any publication, in whole or in part, of information obtained from UMC must include a statement:

- (i) regarding the source of the information,
- (ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
- (iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.

# New vaccines, new challenge?

*Jerry Labadie*

In December 2010 the three West African countries Burkina Faso, Mali and Niger were the first to introduce a revolutionary new conjugate vaccine called MenAfriVac™, a WHO prequalified vaccine (see package insert\*). Nearly 20 million people were immunized with this vaccine in mass campaigns. MenAfriVac protects against meningitis A at a younger age (from one year) and for a longer period than the currently-used vaccines. Meningitis A causes seasonal epidemics in Africa's meningitis belt: 25 countries stretching from Senegal in the west to Ethiopia in the east. MenAfriVac is manufactured by the Serum Institute of India and has been developed by the Meningitis Vaccine Project (MVP), a partnership between the Program for Appropriate Technology in Health (PATH) and World Health Organization.

## Vaccines for developing countries

In the past, the introduction of vaccines in low- and middle-income countries (LMIC) would follow on several years after introduction of the same vaccine in high-income countries. This was beneficial for LMIC which often have limited resources to conduct post-marketing safety monitoring (PMS). LMIC could benefit from effectiveness and safety data that had already been collected and analyzed during years of use in countries better equipped for PMS, mostly during use of the vaccine in national immunization programmes (NIP). MenAfriVac™ is the first of hopefully many vaccines that have been specifically designed and developed to address the infectious disease burden of LMIC. An implicit characteristic of these vaccines is that they will not be implemented on a population scale in high-income countries: there these vaccines will only be used on a small scale - in traveller's clinics but not in NIPs. Consequently post-marketing surveillance of MenAfriVac and future, similar vaccines needs to rely on the surveillance systems in place in the LMIC where these vaccines are introduced and used.

## Surveillance included

Post-marketing surveillance of newly-introduced vaccines in LMIC could be conducted by the NIP and the regulatory authority/ national pharmacovigilance centre, preferably in a concerted effort. Of the three West African countries that have recently introduced MenAfriVac™, Burkina Faso is a member of the WHO Programme for International Drug Monitoring since 2010; Mali and Niger are both associate

members. Burkina Faso piloted the introduction of MenAfriVac with a phased roll-out of the vaccine. This included an initial cohort of 400,000 targeted people with both active surveillance and enhanced spontaneous reporting of adverse events following immunization (AEFI) by Immunization Programme staff.

## Possible collaborations

The introduction of vaccines such as MenAfriVac™ in LMIC countries underlines the need for regulatory authorities, pharmacovigilance centres and immunization programmes to join forces in the surveillance of AEFI. In VigiBase, managed by the UMC, there is an existing repository to store, analyze and share the AEFI data for countries that have limited resources to do so themselves. Last but not least, these introductions should also be the obvious incentive for an associate member to become a full member of the WHO Programme for International Drug Monitoring.

## Effectiveness

In a June 9, 2011 press release the WHO reports high effectiveness of the vaccine: "With the 2010–2011 epidemic season largely over, WHO surveillance data show just four confirmed cases of meningitis A in Burkina Faso, the first country to introduce the vaccine nationwide. No confirmed cases were reported in Mali, while four cases were reported in Niger, all in unvaccinated individuals". New campaigns will begin in Cameroon, Chad, and Nigeria. Nearly 65 million people overall are expected to have received the MenAfriVac vaccine by the end of the year".

\*[http://www.who.int/immunization\\_standards/vaccine\\_quality/MenAfriVac\\_SII\\_insert.pdf](http://www.who.int/immunization_standards/vaccine_quality/MenAfriVac_SII_insert.pdf)

## GACVS

The Global Advisory Committee on Vaccine Safety (GACVS) held its 24<sup>th</sup> meeting in Geneva (Switzerland) on 16–17 June 2011.

It reviewed or examined the following:

1. Meningitis A conjugate vaccine – first 20 million doses (see main report)
2. Global vaccine safety Blueprint
3. Background rates of vaccine adverse events
4. Classification for vaccine safety causality assessment

The full report of the meetings are downloadable from <http://www.who.int/wer/2011/en/>

GACVS meets twice a year, in December and June, followed by meeting reports in the *World Epidemiological Record* from WHO.

## Lareb reaches 20

Linda Härmark

On March 17<sup>th</sup> the Netherlands Pharmacovigilance Centre Lareb celebrated its 20<sup>th</sup> anniversary in an old monastery in the village of Vught, close to the Lareb headquarters in 's-Hertogenbosch. Current and old employees as well as old members of the board and scientific advisory board and those who have worked close together with Lareb for the past 20 years were invited.

Around 100 people attended the event which had the theme of looking back – and looking forward.

The first speaker was dr Fred de Koning who was the founder of the first regional pharmacovigilance office in the 1980s. He gave an interesting and entertaining talk about how a spontaneous reporting system was set up by pharmacists and general practitioners. The concept of regional pharmacovigilance offices spread throughout the Netherlands. In 1991 these regional

offices were bundled in one national organization, Lareb.

June Raine, Director of Vigilance and Risk Management at the UK Medicines and Healthcare products Regulatory Agency and chairman of the Pharmacovigilance Working Party at the European Medicines Agency was our invited speaker. She talked about spontaneous reporting as a basis of pharmacovigilance and how important and valuable these reports are, especially in a world where record-linkage and pharmaco-epidemiological database studies attract more and more attention.

Florence van Hunsel gave a presentation about the role of patients in pharmacovigilance, a topic that is getting more attention in the European Union since competent authorities will have to implement patient reporting according to the new EU pharmacovigilance legislation.

At the end of the afternoon a representative from the Ministry of Health talked about the role of the government in pharmacovigilance and Bert Leufkens, chairman of the Dutch Medicines Evaluation Board talked about the role of Europe and the role of national drug regulatory authorities. Finally, Kees van Grootheest, director of Lareb, talked about how Lareb should proceed in the future. As a result of new EU pharmacovigilance legislation but also due to other developments, pharmacovigilance is changing. Lareb has played an important role in the past in Dutch pharmacovigilance and will hopefully continue doing so in the next 20 years.



Kees van Grootheest, Fred Dijker (chairman of the Lareb board), Fred de Koning and his wife at the 20th anniversary of Lareb

## ISoP Training course in Minsk

Helena Wilmar



Richard Hill (UMC), Aliksandr Sherakou (NC Head), Marie Lindquist (UMC), Svetlana Setkina (NC), Alla Kuchko (NC), Helena Wilmar (UMC)

For the first time, an ISoP training course has been organized in a CIS country (Commonwealth of Independent States). Two parallel courses 'Reporting, Causality Assessment, Risk Factors and Mechanisms of ADRs' and 'Risk Management and Regulatory Inspections' were held at the Belarusian Medical Academy of Post-Graduate Education in the city of Minsk, Belarus on the 26-27th of May, 2011. The courses attracted around 90 participants.

Since the courses were organized in collaboration with the National Centre (NC) in Belarus (the Center for Examinations and Testing in Health Service – within Ministry of Health), UMC staff (who were acting as presenters and a participant at one of the courses) took the opportunity to pay a short visit to the centre. Discussions were held together with the Director for the whole department, Dr Aliksandr Staliarou, and NC staff.

## Spreading the word in Thailand

Bruce Hugman

### Mature audience

'Communicating risk and drug safety information' was the title of a one-day seminar held by PRoMA\*, the Thai Pharmaceutical Research and Manufacturers' Association, in Bangkok in April. It was organised by Dr Pravich Tanyasittuntorn and led by UMC's communications specialist, Bruce Hugman. Twenty-four participants attended, representing a total of fifteen local and international companies.

### and young

At Rangsit University, in late March, 240 third-year BSc pharmacy students spent a week with Bruce, studying communications skills. This course has now been run for five





*PReMA members and staff at their communications seminar, organiser Dr Tanyasittunton on the left.*

## International Course in Córdoba

*Mariano Madurga*

A 1<sup>st</sup> International Course on Pharmacovigilance in Córdoba, Argentina was held on 6–7 May 2011, organized by the Unified System of Pharmacovigilance of the Province of Córdoba. More than 200 health professionals attended, not only from all over Argentina, but also from Bolivia, Chile, Paraguay and Uruguay; a significant number of students were also present.

Other organizations involved included the College of Pharmacists of Córdoba and the School of Chemistry, the Hospital Pharmacy

section at the National University of Córdoba (UNC) with sponsorship from the Argentinean Pharmaceutical Federation (COFA).

The theoretical and practical programme was presented by the head of the national pharmacovigilance centre, Dr Inès Bignone (Administración Nacional de Medicamentos, Alimentos y Tecnología Médica, ANMAT), Dr Silvia Boni (ANMAT), Dr Ada Sisti (Blood Products Laboratory, UNC), Enrique Roca (the Argentinean Pharmaceutical Federation, COFA), Mercedes Rencoret (College of Pharmacists of Córdoba) and Dr Mariano Madurga (Agencia española de medicamentos y productos sanitarios - AEMPS, Spain). The programme is accessible via

<http://servicios.cofa.org.ar/?CursosN>.

years, along with an additional week on patient counselling skills for fifth-year students.

This series of events represent the growing awareness in Asia, and elsewhere, of the importance of formal recognition of communications as a high priority field in patient safety, and of communications training as an essential element in professional development.

\*[www.prema.or.th](http://www.prema.or.th)

As well as topics such as classification and definitions, pharmacovigilance systems, the WHO International Programme, databases and dictionaries (WHO-ART, MedDRA), monitoring of blood products, biotechnological and vaccines, two workshops were held. The first evaluation workshop was of suspected ADRs in terms of coding and causality assessment, the second workshop assessed the information requested in yellow cards, and possible proposals to change information transmitted to the Argentine Pharmacovigilance System, coordinated by ANMAT. A new step to expand the activity of pharmacovigilance in Argentina.



*The large group attending the Córdoba course*

## A warm welcome in Iceland

*Hanna Pedersen and Richard Hill*

In mid-April, Richard Hill and Hanna Pedersen from Reporting, Analysis & Country Support (RACS) at the UMC had the pleasure to spend two days at the Icelandic Medicines Agency (IMA) in Reykjavik. The purpose of the visit was to meet and to establish a closer collaboration with the centre. We wished to get a better understanding of the pharmacovigilance work performed in Iceland, specific routines around Individual Case Safety Report (ICSR) reporting at the centre and also what kind of support the UMC could provide to the centre.

The Icelandic centre showed great hospitality, starting at the airport where we were met by Hjalti Kristinsson, the responsible person for Pharmacovigilance at IMA. The pharmacovigilance activities are a part of the Inspection unit at IMA, and there are two staff working with ICSR reporting, Hjalti and Særun B. Nielsdóttir.

### High reporting

Despite or perhaps because of its size (population 319,000), Iceland is one of the 'top 20' reporting countries to VigiBase in terms of reports per million population (statistics from UMC website: <http://www.who-umc.org/graphics/24904.jpg>).



*Hjalti Kristinsson, Hanna Pedersen at the Icelandic agency*

On the first day, we were welcomed to the Agency by Rannveig Gunnarsdóttir, Executive Director of IMA. We gave a presentation about post-marketing safety of medicines and the WHO Programme for the staff at IMA and invited guests from the Directorate of Health. Afterwards we gave the same presentation for physicians and pharmacists at the National Hospital in Reykjavik. The

National Hospital is one of the main ADR reporting centres in Iceland, providing about 40% of the reports received by IMA.

The rest of the day was spent at IMA with Hjalti and Haraldur Sigurjónsson, Head of the Inspections Unit. Hjalti made a presentation about ICSR management, Hanna presented the benefits and obligations of being a member of the WHO Programme, and Richard presented the Documentation Grading project (see page 14-15).

The second day started with a step-by-step demonstration of the Icelandic reporting system from Særun, and after that Richard demonstrated the UMC tools VigiSearch and VigiMine. After two days of very fruitful pharmacovigilance discussions, we were invited to the restaurant 'Fiskmarkaðurinn' (Fish Market) for a splendid seafood dinner.

We thank the Icelandic Medicines Agency for hosting us during these two days, and a special thanks to Hjalti for taking such good care of us and for being an excellent guide!

### Results

A month after our visit good news reached us: after discussions between IMA and the National Hospital in Reykjavik, the hospital was appointed as a regional pharmacovigilance centre and an action plan to increase reporting has been scheduled at the hospital. The IMA and the Directorate of Health are also collaborating to increase awareness of adverse reactions, and a letter jointly written by the IMA and the Directorate will be distributed to healthcare professionals very soon. We wish IMA and the National Hospital good luck with this new collaboration!

## Pictograms

*The following message was posted on the pharmaceutical communication exchange system E-drug 27 June 2011. Since it is of relevance to many readers of Uppsala Reports we have obtained permission to reproduce it.*

### Study of pictograms representing undesirable effects of medicines

Dear e-drug community

Icons are a useful communication tool to provide information to patients with limited understanding of the language. To solve this problem, the International Pharmaceutical Federation, in collaboration with the Children's Hospital of Eastern Ontario and Algonquin College in Ottawa, Ontario, Canada, has developed a series of icons representing the main adverse reactions to drugs. We invite you to respond to this questionnaire. We will identify the pictograms best understood by a majority of people around the world. It only takes 10 to 15 minutes. This study is important to improve the safe use of medicines worldwide. To facilitate its implementation, this study was written in several languages

We invite you to complete the questionnaire by clicking on a link below:

English (Anglais, Inglés): [http://www.surveymonkey.com/s/sideeffectspictograms\\_english](http://www.surveymonkey.com/s/sideeffectspictograms_english)

Français (French, Francés): [http://www.surveymonkey.com/s/sideeffectspictograms\\_francais](http://www.surveymonkey.com/s/sideeffectspictograms_francais)

Español (Spanish, Español): [http://www.surveymonkey.com/s/sideeffectspictograms\\_espanol](http://www.surveymonkey.com/s/sideeffectspictograms_espanol)

Thank you in advance for your collaboration.

Salutations

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# Pharmacovigilance challenges in the Rainbow Nation

Sten Olsson

South Africa, called the 'Rainbow Nation' by Archbishop Desmond Tutu, joined the WHO pharmacovigilance programme in 1992. Since then the country has submitted approximately 16,000 ICSRs to VigiBase, almost half (48%) of the total submission from the African continent. The National Pharmacovigilance Centre is hosted by the Medicines Control Council of the National Department of Health in Pretoria, with Mukesh Dheda as the national co-ordinator. The national ICSR database is based at the University of Cape Town with Nanette O'Connor currently managing the Pharmacovigilance Unit in Cape Town.

## A new structure

I had the privilege of spending a day with Mukesh Dheda and his team in Pretoria, including Hellen Moropyane, Linda Thomson and Linh Diep, in May this year. I was told about the imminent restructuring of the South African regulatory authority. One of the many challenges facing the pharmacovigilance programme is the difficulty to recruit and retain competent staff, leading to underperformance of the system. Hope is currently provided by opportunities offered through the South African HIV/AIDS treatment programme in which resources for follow-up of the safety of antiretroviral treatment have been allocated. A decentralized network is being established, by which ICSRs are being collected and analyzed carefully and thoroughly by treatment centres at sub-district level. The reports are then contributing to treatment assessment, immediate patient interventions and follow-up at district level before being submitted to the National Pharmacovigilance Centre for coordinating. The role of the National Pharmacovigilance Centre will be to monitor overall safety patterns and regional differences. Medicine safety monitoring is thus made an integral component of the quality of care assessment.



Pharmacovigilance team at National Control Council, Pretoria. Hellen Moropyane, Linh Diep, Mukesh Dheda and Linda Thomson



Lynette Terblanche, SAAPI chairperson, Mandisa Hela, Registrar of Medicines, Sten Olsson, Melinda Viljoen, conference manager in Johannesburg

The pharmacovigilance system established for the HIV/AIDS treatment programme is expected to be a model and a driver of other pharmacovigilance activities in South Africa.

## Training and guide

Mukesh Dheda and his Public Health Pharmacovigilance team have embarked on a major project to provide pharmacovigilance training to treatment teams at sub-district level. One of the tools used is the 'Antiretroviral Therapy in South Africa: A Pocket Guide on Prevention and Management of Side Effects and Drug Interactions', the second edition of which has been published and is now being widely distributed.

## Harmonization

Among other challenges facing the South African pharmacovigilance programme are to harmonize its data management system with international standards. The desirability of moving to an E2B compatible database is recognized. Such a change, and an adaptation of national requirements for company reporting aligned with international standards, would facilitate the involvement of industry in safety surveillance. Currently, optimum efficiency of the Pharmacovigilance Centre is being significantly frustrated by its not being consulted and sometimes not even informed of various safety studies carried out in the country by NGOs, pharmaceutical companies and academic researchers. Data from such studies are frequently not made available to the authority ostensibly responsible for the integration and monitoring of medicine safety in the country.

## Industry pharmacists

I was also invited by the South African Association of Pharmacists in Industry (SAAPI) to lecture to a pharmacovigilance workshop held in Johannesburg on 24 May 2011. The opening address was given by Ms Mandisa Hela, Registrar of Medicines of the Medicines Control Council in South Africa, and Mukesh



South African Pocket Guide on Prevention and Management of Side Effects and Drug Interactions

Dheda presented the model of decentralized pharmacovigilance outlined above. I contributed with a description of the WHO Pharmacovigilance Programme and relevant ICH guidelines. The workshop's programme also covered signal analysis, risk management plans and pharmacovigilance audits.

# The latest pharmacovigilantes!

*Anna Hegerius*

On a chilly evening on the first of May, a group of excited people from all over the world gathered at a small and cosy hotel in Uppsala. It was the welcome reception and start of the UMC's 13<sup>th</sup> international pharmacovigilance course. There is usually much competition for places, and this year was no different. Only a third of all applicants could get a place and it was a difficult selection process. It turned out to be a well-chosen group of people however, since the team spirit and friendliness among the final participants were truly amazing! The majority of the group consisted of staff from regulatory authorities, but the pharmaceutical industry and some other institutions were also represented.

## What's new?

Although the essence of the course remained the same, there were a number of important changes this year. To name a few, a new main venue was used and it was perfect for the course. The participants were also served lunch at a cafeteria nearby, instead of having to find a place to eat themselves. Bruce Hugman (UMC communications consultant) was the main facilitator of the first module and made sure that everyone knew what to do, where to be and ensured all the participants were involved in interactions during and after each session. Another major improvement, both for the course administration and the participants, was the launching of the course website. It is a restricted sub site at the UMC Collaboration

Portal (like Vigimed) where all course material can be easily uploaded. All pre-course reading material and practical information was shared on this site to which the participants had immediate access. Finally, almost all the presentations were recorded during this course. Once the videos have been edited and approved, they will be available via a link on the UMC website together with a statement on their intended use.

## Theory and practice

The course is intended primarily to support the development of programmes for spontaneous adverse reaction reporting and to give an introduction to other methodologies. As before, the course consisted of different modules.



*African group discussion on patient safety*



*Jitendra Kumar and Adielia Saldaña handing over the 'thank you' poster*



*Happy dinner*



*Dr. Pia Caduff running an interactive session*



*Course participants with Prof. Bert Leufkens*



*Course participants assembled outside the hotel*

The first module, common for all participants (over seven days), dealt with many aspects of pharmacovigilance in general, both theoretical and practical. The theoretical parts consisted of lectures and group discussions. Practical sessions included the recording of case information in VigiFlow and retrieval of case information from VigiBase using the tools VigiSearch/VigiMine. There was also one-day of parallel sessions; the company representatives learnt about regulations, Periodic Safety Update Reports and Risk Management Plans to meet their specific needs, while the participants from regulatory agencies discussed how to establish a pharmacovigilance centre and how to design effective ADR reporting forms.

After the first module, most of the group stayed on and quite a few additional participants arrived to take part in one of the two second modules (each over three days) that focused on pharmacoepidemiology and effective communications, respectively.

The principal faculty during the two weeks consisted of UMC staff as well as experts

from other organisations: WHO Headquarters, the WHO Collaborating Centre for Advocacy & Training in Pharmacovigilance (Ghana), the Medical Products Agency (Sweden), Swissmedic, the Patient Safety Unit for Copenhagen Region (Denmark), Utrecht University (The Netherlands), Karolinska Institute (Sweden), Elliot Brown Consulting (UK) and Empower School of Health (India).

**Being social**

Building valuable new relations with other course participants and having a great time is as important as the scientific part of the training course. A number of social events were arranged, including an official course dinner and the opportunity to visit the UMC office in the evenings. The dinner took place in the ancient Orangery in the Linnaeus garden, where the famous botanist Carl von Linné once lived. In addition to delicious food and good company, the dinner guests listened to a harpist and Linné himself even paid a visit and gave a long and very amusing speech about his exploits. Among unofficial social activities, there were rumours that traditional singing and dancing lessons were

being held in the dining room of the hotel. This was later confirmed by interesting pictures that appeared on the Facebook page that the participants had created even before leaving Uppsala.

**...and the result?**

The general opinion about the course was very positive in spite of the heavy programme. During the closing ceremony, the UMC Director Marie Lindquist, proudly handed out the course certificates. The participants then thanked the UMC for organizing the course, via a lovely speech in Spanish which was later translated to English. They had also written 'thank you' in all their languages on a big poster which was handed over to Marie. It was wonderful to observe how all these people, until recently complete strangers, had formed such strong bonds in only two weeks. They left Uppsala exhausted but with new ideas, friendships and enthusiasm. It will be exciting to follow the progress in their respective countries as a result of their acquired knowledge, experience and strengthened commitment to patient safety.



Guests with famous Linné



Course participants assembled in the main course venue



Prof. Ralph Edwards showing the logic of causality

# Documentation grading – how complete are the reports?

Sara-Lisa Fors

Several countries have expressed a wish for feedback regarding the Individual Case Safety Reports (ICSRs) they send to VigiBase, and as a result the UMC has developed, and recently started communicating, the result of the Documentation grading Completeness score.

Documentation grading was developed by the UMC's Research and Pharmacovigilance Departments to measure the amount and quality of the information provided on ICSRs as they appear in VigiBase. Documentation grading consists of two parameters: Completeness and Relevance. Completeness is a quantitative measure describing the amount of information present in an ICSR. Relevance is a qualitative measure aiming to identify information that may strengthen causal associations between a drug and an adverse drug reaction in the ICSR. While the

parameter Relevance is still under development, the Completeness score is now implemented in VigiBase.

In January a pilot version of the Completeness score was sent out to seven national agencies for evaluation. Their comments were positive and some of the countries also had valuable suggestions for improvements and clarifications. After taking into account the feedback received, the first official version was launched and in June the UMC Country Support Team started sending the results to the reporting countries.

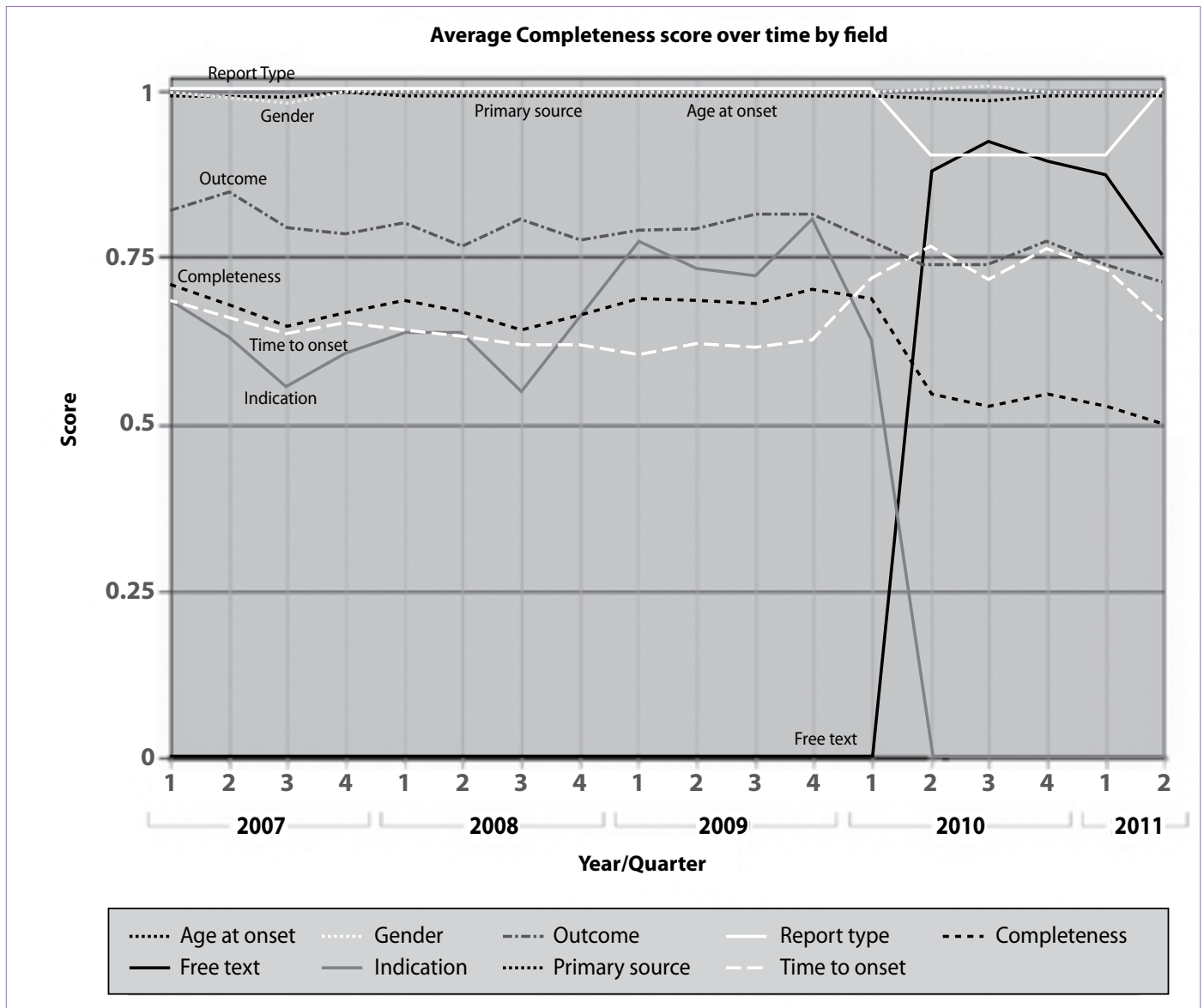
Although National Centres are dependent on their reporters for the quality of reports received, we believe that it is of interest for National Centres to know how report completeness has varied over time and to

investigate possible reasons for this. Some issues that we expect to identify include problems with the process of extracting and sending ICSRs to UMC, and differences that emerge when a country changes its ICSR database or reporting format (for example, from INTDIS to ICH-E2B<sup>1</sup>).

By communicating the results to the National Centres, our hope is that issues with the quantity and quality of information in ICSRs will be identified and, as far as possible, rectified, which in the end will lead to increased usefulness of the reports in VigiBase.

Anyone interested in more information about the documentation grading may contact us at [vigibase@who-umc.org](mailto:vigibase@who-umc.org). We also welcome any comments or suggestions for further improvements.

Graph 1. An example from one country, showing all elements of information that affect the average completeness over time.

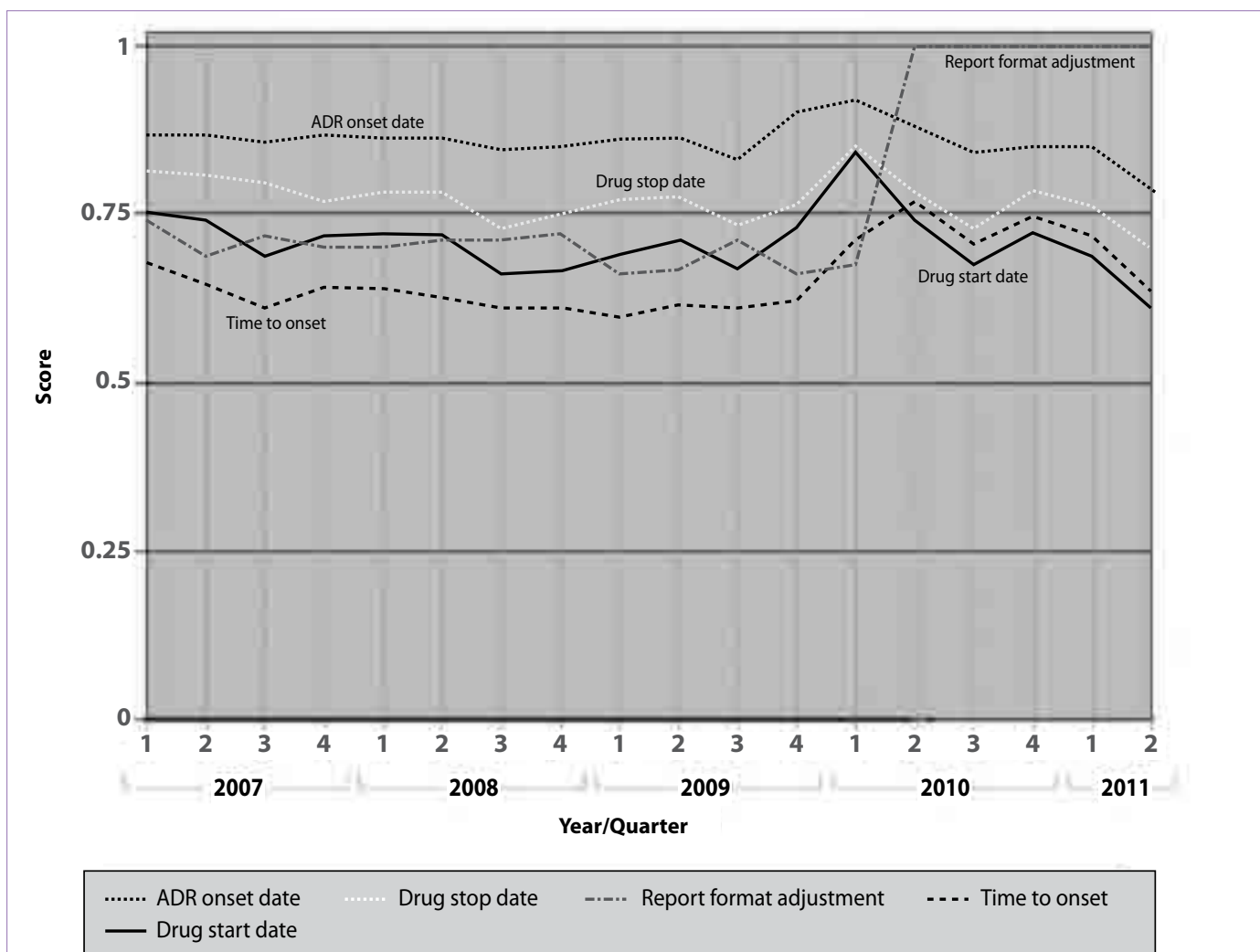


Age at onset	A change in score might be due to a change in information in one of the following fields; "patient onset age", "patient onset age unit", "patient birth date", "age group" and/or "ADR date of onset". To investigate a change in the score look at "Completeness score over time - AgeAtOnset".
Gender	A full score is given if an allowed value (male or female) has been entered.
Indication	A full score is given if an allowed value has been entered. Since Indication is reported on drug level, the score per ICSR is the average score of all suspected/interacting drugs.
Primary source	A full score is given if an allowed value has been entered.
Outcome	A full score is given if an allowed value has been entered. Since Outcome is reported on ADR level in E2B, the score per ICSR is the average score of all ADRs.
Free text	A full score is given if an allowed value in any free text field has been entered.
Report type	A full score is given if an allowed value has been entered.
Time to onset	A change in score might be due to a change in information in one of the following fields; "Drug Start Date" and/or "ADR date of onset".
Completeness	Average Completeness calculated from the pieces of information above.

Note the great change in indication and free text in the second quarter 2010 (in Graph 1) which is connected to a change of reporting format (from INTDIS to ICH-E2B) by the country in question. Since this change we have not received any indications, but on most reports we do receive free text in at least one of the many E2B-free text fields, such as patientmedicalhistorytext, reportercomment, sendercomment, narrativeincludeclinical etc.

1 The UMC accepts two different electronic ICSR transmission formats; E2B and INTDIS. The recommended format is the ICH standard, E2B. The old WHO-format, INTDIS, is no longer recommended but still accepted during a transition period.

Graph 2: Average completeness over time – time to onset. This illustrates the information affecting one of the above elements time to onset, which is measured as the time difference between the drug start date and ADR date of onset for the same example country used in Graph 1.



ADR onset date	Scoring 2009-12-14 = 1.0 (year - month - day) 2009-12 = 0.5 (year - month) 2009 = 0.25 (year)
Drug start date	Scoring: see ADR onset date
Drug stop date	Scoring: see ADR onset date
Report format adjustment	INTDIS reports with more than one ADR receive a 50% reduction in Time To Onset score since the ADR onset date is reported per report not per ADR.
Time to onset	A change in score might be due to a change in information in one of the following fields; "Drug Start Date" and/or "ADR date of onset".

# Complementing existing pharmacovigilance methods

Ennita Nilsson and Sharon Ako-Adounvo

A course to introduce additional pharmacovigilance methods in an African setting to complement data from existing methods was recently organised as part of the Monitoring Medicines project. The Pharmacy and Poisons Board (PPB) in Kenya and WHO organised this memorable training course from 11-19 June 2011, in collaboration with FP7 partners including the UMC, University of Ghana Medical School and Copenhagen HIV Programme.



The keen group of pharmacovigilantes assembled in Mombasa

Participants from Kenya, Burkina Faso, Botswana, Zimbabwe, Ethiopia and Uganda, and a pool of pharmacovigilance experts converged on the Travellers Beach Hotel, Mombasa, Kenya with the aim to develop appropriate pharmacovigilance systems, incorporating both active and spontaneous surveillance methods, to address national drug safety priorities. Experts introduced and further developed Cohort Event Monitoring (CEM) for Malaria and Targeted Spontaneous Reporting (TSR) for HIV treatment programmes.

## Intense six days

At the end of the six-day training, participants became familiar with CEM and TSR methodologies and their implementation. Participants from respective countries were tasked with developing a country plan to submit to WHO in order to access European Commission funding set aside for the implementation of CEM and TSR (for anti-malarials and anti-retrovirals). Two successful country plans, one for each method will be funded for one year. The selected countries will pilot the adaptation and implementation for meeting disease-specific pharmacovigilance objectives using one of the methods. They will collect reports of adverse events or suspected reactions in patients treated with medicines for malaria or HIV/AIDS, using CEM and TSR methods.

## Background

Spontaneous reporting systems are the easiest to establish and the cheapest to run, but reporting rates are generally very low and subject to strong biases, and there is no database of all drug users or knowledge of overall drug use. These problems hinder accurate and timely assessment of the extent of risk, risk factors, or comparisons between drugs. Pharmacovigilance experts are agreed that other methods are needed to improve the ability to measure quantitative aspects of medicine safety, identify specific risk factors and groups, and provide valid clinical characteristics of the problems associated with medicines use.

## Cohort Event Monitoring (CEM)

WHO has adapted the broad principles of the New Zealand Intensive Medicines Monitoring Programme (IMMP) for use in public health

programmes, the Cohort Event Monitoring (CEM) method. CEM was proposed as a complement to spontaneous reporting systems when there is a need for the prospective and proactive recording of adverse events associated with one or more medicines. It is essentially an observational method for monitoring a new medicine in the early post-marketing phase.

## Targeted Spontaneous Reporting (TSR)

Novel workable approaches are being sought to strengthen the spontaneous reporting systems that already exist, when there is a need for the prospective and proactive recording of adverse events associated with one or more medicines. TSR is a form of spontaneous reporting but carried out in a targeted manner in a cohort of patients e.g. to patients who report to specified health facilities on a regular basis. Its precise operations are undergoing rapid revision and will be finalised during the pilot programme.

'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes', started in September 2009, and will run for a further 2½ years. 'Monitoring Medicines' (the project's short name) was developed by WHO and is coordinated by the Uppsala Monitoring Centre, with funds from the European Commission (Seventh Framework Programme (FP-7) of the Research Directorate).

# First reporting period approved by the European Commission

Ennita Nilsson

The Monitoring Medicines project submitted its first report (September 2009 – February 2011) to the European Commission (EC) in April 2011. On the 16<sup>th</sup> of May, the management team received wonderful news that on the basis of the periodic reports submitted to the Commission and results obtained to date, the research may continue as specified.

Upon receiving the news Sten Olsson, the Project Coordinator, informed all partners and colleagues and a toast was shared with some (via telephone).

## Deliverables achieved in the first period

The project has so far developed

- its own website ([www.monitoringmedicines.org](http://www.monitoringmedicines.org))
- a situation analysis regarding consumer reporting of medicine-related problems
- training and capacity building of national pharmacovigilance centres for minimizing preventable harms from medicines (held in Rabat)

- methods for identifying substandard and counterfeit products and dependence liability of medicines in the WHO ICSR database, and
- training in pharmacovigilance methods that complement spontaneous reporting.

The project continues to implement its plans for the remaining deliverables due to be reported in September 2012.



# Academic appraisal of UMC research

Ola Caster

UMC researcher Ola Caster successfully defended his licentiate thesis *Detecting drug risks and weighing them against benefit – Statistical and decision-analytical approaches* on 6<sup>th</sup> May 2011, at the Department of Computer and Systems Sciences, Stockholm University. The licentiate degree in Sweden is placed in between the master and doctor degrees, and this thesis was written as part of Ola's PhD studies at Stockholm University. His main supervisor is Professor Love Ekenberg, and former director Ralph Edwards is co-advising from UMC's side.

As suggested by its title, the thesis connects recent UMC research within two themes of importance in pharmacovigilance. The first theme relates to detecting and evaluating previously unknown risks with drugs, specifically from large databases of individual case reports, such as VigiBase. The second theme concerns the subsequent assessment of such signals of risk within the wider context of a drug's other effects – beneficial as well as adverse – ideally in relation to other relevant drugs and the disease to be treated. The former theme is considered in papers I and II, and the latter in papers III and IV. (For a list of the included papers, see box.)



## Regression and causality reflections in adverse drug reaction surveillance

The challenges of post-marketing adverse drug reaction (ADR) surveillance based on individual case reports are plentiful. To mention two, reports are generally collected in an unsystematic manner, and reporting rates can be massive. Paper I considers two specific issues with currently used methods for automatic screening of large databases to detect potentially causal drug-ADR

associations. These issues are of a quite technical nature, but both relate to the impact from other reported drugs on relevant reporting rates for a drug-ADR pair currently under consideration. The paper demonstrates the use of so-called shrinkage regression as an alternative method to mitigate these problems. It is concluded that the novel method brings added value and should be further considered as a complement to existing methods. However, its complexity is too great, and its performance not so outstanding to recommend it as a replacement.

This is followed in paper II with a conceptual discussion on causality in pharmacovigilance, in particular regarding the piecing together of different sources of evidence when considering a potential signal. This forms a bridge between the automatically highlighted potential signals in paper I and papers III and IV on benefit-risk assessment, as such assessments can only consider risks whose evidence has been evaluated for causality. Paper II contains some possibly controversial thoughts on the value of individual case reports.

## Benefit-risk assessment

The second part of the thesis examines the incorporation of a newly detected emerging drug risk into a wider benefit-risk assessment context. This is important to facilitate decisions on what to do with an emerging risk, both through regulatory actions, and in terms of treating individual patients. It is important also to get a sense of the significance of a particular signal. However, such benefit-risk assessments are challenging as they need to incorporate heterogeneous information that may also be inaccurate or even deficient. In the post-marketing setting one also needs to factor in the question of urgency: decisions need to be made quickly, and cannot await further information collection or unduly time-consuming analyses.

A novel quantitative approach attempting to face these challenges is presented in paper IV, building on general method developments in paper III. This approach is based on so-called 'probabilistic decision analysis'. It incorporates into its quantitative framework whatever widely agreed upon qualitative information there is to relate the possible outcomes of various treatment alternatives to each other. It is therefore quick and relatively easy to use, hence well suited for

emerging post-marketing risks. Paper IV describes the methodology and compares it to a standard approach on three available case studies. The results are promising, showing that even very straightforward information can be sufficient to reach a conclusion. Our novel method was overall concordant with the reference method, but could also highlight new and very interesting aspects, in particular for one of the case studies.

## Future prospects

This thesis primarily presents novel methods together with preliminary investigations to support their usefulness. Key tasks for the future are to test them more carefully in practice, and in the longer perspective to implement them routinely.

- I Caster O, Norén GN, Madigan D and Bate A. Large-Scale Regression-Based Pattern Discovery: The Example of Screening the WHO Global Drug Safety Database. *Statistical Analysis and Data Mining*, 2010. 3(4): p. 197-208.
- II Caster O and Edwards IR. Reflections on Attribution and Decisions in Pharmacovigilance. *Drug Safety*, 2010. 33(10): p. 805-809.
- III Caster O and Ekenberg L. Combining Belief Distributions with Qualitative Statements in Decision Analysis, in *Coping with Uncertainty: Managing Safety of Heterogeneous Systems*, Y. Ermoliev, K. Marti, and M. Makowski, Editors. [To appear in a forthcoming volume of the Springer series *Lecture Notes in Economics and Mathematical Systems*.]
- IV Caster O, Norén GN, Ekenberg L and Edwards IR. Quantitative benefit-risk assessment using only qualitative information on utilities. [Submitted for publication.]

# Paediatric Safety

Kristina Star

One of the UMC Research Department's focus areas is on paediatric safety. Special considerations are needed when using medicines for children. There are several reasons for this:

- Individuals undergo immense physiological and psychological changes during childhood – most physiological developmental changes in drug absorption, distribution, metabolism and excretion occur during the first 2 years of life.<sup>[1, 2]</sup>
- Weight and body size change greatly during childhood, resulting in the need for individualised dosing.
- The availability of suitable dose formulations for the growing child is necessary in order to administer but also to prescribe appropriate doses for children.<sup>[3]</sup>
- Optimal dosing of a medicine is important to prevent adverse drug reactions (ADRs).
- The knowledge of a medicine's effect and safety in children can be limited, because not all medicines used in children have been tested in this population.<sup>[4, 5]</sup>
- Children can react differently to medicines compared with adults.<sup>[6]</sup>

## Global perspective

The benefits of global collaboration and collections of individual case safety reports are obvious when it comes to the paediatric population. This became apparent already in the 1960s, resulting from the thalidomide crisis. In a review of WHO signals between 1998 and 2008, only 4% of the signals concerned paediatrics, with problems in

newborns resulting from mother exposure of antidepressants and in children receiving vaccines, psychostimulants, herbals, and beta-2-adrenoceptor agonists (internal UMC evaluation). Several of these signals had not been generated through our routine signal detection process, which is focused on newly-marketed substances. Many of the drugs used for children are old drugs. We also exclude known problems in our process, though a known problem in an adult might have a different characteristic in a child and present itself with a different benefit risk profile. There is a possibility that this could limit the recognition of important problems reported for children.

## New methods

We have therefore recently started to work on developing methods and processes to detect previously unknown ADRs in the child population and to characterize ADRs in children.<sup>[7]</sup> To get a sense of what events have been reported for children, we reviewed VigiBase reports for ages 0-17 years (excluding vaccine reports) and contrasted the overall reporting pattern with the adult reports. We also studied what type of adverse reactions had been reported more frequently during recent years for different child age groups.<sup>[8]</sup> We found that 8% of the non-vaccine reports in VigiBase were for ages 0-17 years, more reports were found for boys (53%) among the children, compared with adults where more reports have been received for women (61%). There was also a higher proportion of reports for children among Latin American and Caribbean (15%), African (15%) and Asian reports (14%) compared with the rest of the world (7%). Reports with medication error-related terms were more frequently reported during recent years, particularly for the younger children.

## Collaboration

In this extension of its research focus, UMC is very pleased to collaborate with paediatric experts at the School of Pharmacy, University of London and Professor Ian Chi Kei Wong, who is the Director and Professor of Paediatric Medicines Research, Centre for Paediatric Pharmacy Research.

1. European Medicines Agency. ICH Topic E 11. Clinical Investigation of Medicinal Products in the Paediatric Population. January 2001 CPMP/ICH/2711/99. [cited 2009 June 10]; Available from: <http://www.ema.europa.eu/pdfs/human/ich/271199en.pdf>.
2. Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med*. 2003 Sep 18;349(12):1157-67.
3. Star K, Caster O, Bate A, Edwards IR. Dose Variations Associated with Formulations of NSAID Prescriptions for Children: A Descriptive Analysis of Electronic Health Records in the UK. *Drug Safety*. 2011 Apr 1;34(4):307-17.
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6. Choonara I, Gill A, Nunn A. Drug toxicity and surveillance in children. *Br J Clin Pharmacol*. 1996 Oct;42(4):407-10.
7. Star K. Detecting unexpected adverse drug reactions in children. *Paediatr Drugs*. 2011 Apr 1;13(2):71-3.
8. Star K, Norén GN, Nordin K, Edwards IR. Suspected Adverse Drug Reactions Reported For Children Worldwide: An Exploratory Study Using VigiBase. *Drug Safety*. 2011 May 1;34(5):415-28.

# Research programme in Drug Safety Science

Geoffrey Bowring

The Department of Pharmaceutical Biosciences within the Faculty of Pharmacy at Uppsala University has recently advertised for a research scientist to create a programme in Drug Safety Science, with a focus on advanced research.

The announcement notes that "in the initial phase of recruitment the Faculty is open with regard to the direction of the future research programme in Drug Safety Science.

One possible research direction of interest at the Faculty could focus on mechanisms of adverse effects, because mechanistic understanding is essential for improving safety assessment. Research focusing on mechanism-based risk assessment or more clinically directed research, such as pharmacovigilance would also be of interest".

A *Letter of Interest*, including CV, may be sent to: [Marianne.Danersund@farmbio.uu.se](mailto:Marianne.Danersund@farmbio.uu.se)

(mark 'Letter of Interest') at Uppsala University, Department of Pharmaceutical Biosciences.

See also [www.farmbio.uu.se](http://www.farmbio.uu.se) and [www.farmfak.uu.se](http://www.farmfak.uu.se)

# David W J Clark, 1940–2011

## Remembering a staunch supporter of pharmacovigilance

*Ruth Savage*

David Clark will be greatly missed by many of us connected with the UMC. He was one of the longest serving and most diligent members of the Signal Review Team. As a pharmacologist he had a long career in the Department of Pharmacology of the University of Otago, New Zealand. More recently he held an appointment with the New Zealand's Intensive Medicines Monitoring Programme. He was an honorary consultant to the UMC and a member of the honorary editorial board of Drug Safety.



Thinking of David, the qualities that immediately spring to mind are kindness, helpfulness, and enthusiasm. Underlying these were a huge depth and breadth of pharmacological knowledge and a constantly enquiring mind, eager to learn about and address new challenges. This enthusiasm and freshness made him an excellent teacher for undergraduates, postgraduates and his contemporaries up to and beyond his retirement.

After his Bachelor of Science and Master of Pharmacy with First Class Honours he went on to obtain a Doctorate in Pharmacology. Early work was in basic autonomic and biogenic amine pharmacology. However, he

became aware of growing concerns about adverse drug reactions. He recalled, on leaving school, as a pharmacy apprentice he dispensed medicines later found to have significant adverse effects, and was given samples of thalidomide with the advice that it was free from side effects. His publications showed a developing interest in adverse reactions, especially underlying mechanisms, which led to an interest in their pharmacogenetic basis. He also published work on patients' understanding of their medicines, contributing to more rational prescribing of agents such as non-steroidal anti-inflammatories and bronchodilators. He later tackled controversial issues surrounding COX-2 inhibitors and long-acting beta agonists.

Collaboration with clinical colleagues in the New Zealand Centre for Adverse Reactions Monitoring, lead to publications of joint work with Ralph Edwards when he was Director, and eventually an appointment within the Intensive Medicines Monitoring Programme (IMMP), working with David Coulter and later Mira Harrison-Woolrych. His major contribution was exploring potential mechanisms for adverse reactions signalled including pharmacogenetic aspects.

David undertook numerous assessments for the UMC resulting in 18 signals for Signal, a number of which led to publications in peer-review journals. He saw the value of closer links between local and global pharmacovigilance and his signals included those detected at a local level through the

IMMP, or spontaneous reports with supporting evidence from Vigibase. He also wrote major review articles.

David was remarkable for his humility. Speaking at the Festschrift on the occasion of his retirement, he didn't talk about his own work, but about the controversial issues in pharmacovigilance that had fascinated him during his lifetime. Contributions are not always measured in research outputs. Colleagues will remember that birthdays and celebrations were always enhanced by David's fine bass voice. He loved singing and participating in amateur operatic productions.

During David's last years he had to cope with a progressive and extremely disabling illness. Our sympathies are with his partner Shona, and also our gratitude; he would not have been able to contribute to pharmacovigilance throughout his illness without her devoted care.

Through his illness we saw another quality – his fortitude. He never complained, but focussed on adapting and did whatever he could for himself. The evening before he died he was discussing a paper with a postgraduate student – a teacher to the end, passing on the baton of pharmacovigilance.

David will be missed by colleagues throughout the world, especially those who were his students.

## A view on forms

*Geoffrey Bowring*

During the 2011 UMC pharmacovigilance course (see pages 12–13) students were asked to display their country's ADR reporting form and to analyze strengths and weaknesses of all the forms. These varied from simple, clean designs to densely-printed multi-page formats. There was also the opportunity to look at the approach of other WHO Programme member countries around the world.

The importance of a well-designed reporting form is often forgotten, and the display and discussion gave much food for thought. The

UMC keeps a collection of national reporting forms – currently over 50.



*The good, bad and ugly: ADR reporting forms on display during the UMC's course*

# New publications

Geoffrey Bowring

## Safety in children

Three new articles on paediatric safety have recently been published.

Detecting Unexpected Adverse Drug Reactions in Children.

Star K.

*Pediatric Drugs*. 2011; 13(2):71-73.

This editorial aims to describe Vigibase™ in the context of paediatric ADRs. The authors set out the origin of UMC data (thus describing a case report in detail) and very briefly introduce the work being undertaken within paediatric safety at the UMC.

Dose Variations Associated with Formulations of NSAID Prescriptions for Children: A Descriptive Analysis of Electronic Health Records in the UK.

Star K, Caster O, Bate A, Edwards IR.

*Drug Safety*. 2011;34(4): 307-17.

This study, based on IMS prescription data, investigated what could influence dose variations of NSAIDs prescribed to children from 2 to 11 years of age. It found that dosage form and, more specifically, tablets/capsules were prescribed in a higher dose than suspension or syrup (liquid) prescriptions.

Suspected Adverse Drug Reactions Reported For Children Worldwide: An Exploratory Study Using VigiBase

Star K, Norén GN, Nordin K and Edwards IR.

*Drug Safety*, 2011; 34(5): 415-428.

This publication reviews child reports in VigiBase by contrasting them with adult reports while also reviewing ADRs by child age groups. The study aims to increase understanding of what reports on children are contained in VigiBase.

See also the article 'Paediatric Safety' by Kristina Star on page 18.

## Reporting of ADRs for anti-malarials

Andrea Kuemmerle, Alex NO Doodoo, Sten Olsson, Jan Van Erps, Christian Burri, Paul S Lalvani.

Assessment of global reporting of adverse drug reactions for anti-malarials, including artemisinin based combination therapy, to the WHO Programme for International Drug Monitoring.

*Malaria Journal* 2011, 10:57

<http://www.malariajournal.com/content/10/1/57>

This article in *Malaria Journal* describes a project profiling the provenance of the pharmacovigilance reporting of all anti-malarials (including ACT) to the WHO adverse drug reaction (ADR) database (Vigibase) during the last 40 years. The paper highlights low reporting of ADRs to anti-malarials and the high number of reports submitted by non-endemic and/or high-income countries.

National pharmacovigilance centres and other organizations are encouraged to create short- and long-term solutions to help tackle the lag between the growing use of ACT and low ADR reporting.

## World Medicines

The World Medicines Situation 2011, 3<sup>rd</sup> Edition

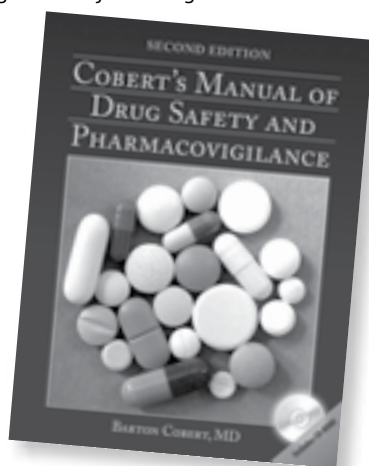
[http://www.who.int/medicines/areas/policy/world\\_medicines\\_situation/en/](http://www.who.int/medicines/areas/policy/world_medicines_situation/en/)

A very useful resume of the current position of medicines safety globally, with references and a glossary. Chapter 12 concerns pharmacovigilance.

## Manual of Drug Safety & Pharmacovigilance

Sten Olsson

In April 2011 the 2<sup>nd</sup> edition of *Cobert's Manual of Drug Safety & Pharmacovigilance* was published by Jones & Bartlett Learning. ISBN-13: 9780763791599, Paperback 408 pages. [www.jblearning.com](http://www.jblearning.com)



Within its own terms of reference this book is very rich. It is a useful handbook for the pharmacovigilance professional working in a

pharmaceutical company or regulatory authority in USA or the European Union and possibly Australia or Canada. Although not made explicit, these professionals constitute the target audience of the book. Over 400 pages and 54 chapters it provides a comprehensive account, with numerous references, of the activities, processes and documents needed to meet the requirements of rules and regulations in the areas mentioned.

However, the title of the book is somewhat misleading; the reader is given the impression that by following all the rules and regulations all demands of pharmacovigilance will be met. In my opinion pharmacovigilance is first and foremost about patient safety. There is no place for the patient perspective or the importance of pharmacovigilance in clinical practice in this book. There is little mention of the challenges to patient safety posed by medication errors, substandard or counterfeit medicines or safety monitoring within mass treatment campaigns and public health programmes. One gets the impression that pharmacovigilance is an administrative activity where compliance with rules replaces intellectual effort and judgment. The aim of pharmacovigilance seems to be to keep a company or regulator free from criticism or harm. The more important questions – whether compliance with regulations will ensure that unexpected harm to patients will be discovered, and whether patients will always get the most appropriate treatment – are not answered. Sadly, few books in pharmacovigilance cover the wide scope of the science and activities beyond regulation.

## Editorials in Drug Safety

There have also been more challenging editorials from the UMC's Medical Advisor Ralph Edwards in *Drug Safety* over the last few months:

Pharmacovigilance and the Null Hypothesis: Do We do Much for Public Health?

Edwards, IR; Isah, A.

*Drug Safety*. 34(2):93-96, February 1, 2011.

Social Media and Networks in Pharmacovigilance: Boon or Bane?

Edwards, IR; Lindquist, M.

*Drug Safety*. 34(4):267-271, April 1, 2011.

Fraudulent and Substandard Medicines: Getting Away with Murder?

Edwards, IR.

*Drug Safety*. 34(6):445-448, June 1, 2011.

## PROTECT Work Package 3

*Ghazaleh Khodabakhshi*

On the 23-24<sup>th</sup> of May, the UMC was host to a delegation from the Work Package 3 of the Pharmacoepidemiological Research on Outcomes of Therapeutics (PROTECT) project. Eighteen European researchers braved the ash clouds in order to gather for a face-to-face meeting on the progress of our work on methods for signal detection.

The overall objective of Work Package 3 is to assess existing methods, and develop new ones, for signal detection from spontaneous reports, electronic health records and clinical trials. A wide variety of medical authorities as well as the pharmaceutical industry was represented at the meeting. There were two intense days of updates and reporting from each of the twelve Work Package 3 sub-packages. A joint dinner at the 'Lingon' restaurant offered an opportunity to network with our European colleagues.



*Members of the PROTECT Work Package 3 in Uppsala in May*

## Safety campaigners

*Sten Olsson*



*Ulf Jonasson*

Ulf Jonasson came to visit the UMC on 12 May 2011. He and his wife Birgitta have spent many years of their professional lives to document the dangers of widespread use of the analgesic substance dextropropoxyphene. They have each produced a PhD thesis to credibly document facts and discuss findings:

*Studies on Dextropropoxyphene with Special Reference to Dependency Among Chronic Pain Patients, Classification of the Manner of Death in Fatal Poisonings, and Characteristics of the Fatal Poisoning Victims*, Birgitta Jonasson, 2000.

*Studies on the Use of Dextropropoxyphene from a Public Health Perspective. Impact of a Regulatory System*, Ulf Jonasson, 2001.

The relentless campaigning by Ulf and Birgitta Jonasson has actively contributed to the gradual phasing out of dextropropoxyphene-containing products from European, American and many other pharmaceutical markets.

## Luisa in Uppsala

*Elki Sollenbring*



*Luisa with Elki*

In May we were delighted to welcome for a short visit Luisa Helena Valdivieso of the Pharmacovigilance Centre at the Faculty of Pharmacy of the Universidad Central de Venezuela in Caracas.



*Sujith Chandy*

## Visit from Vellore

*Sten Olsson*

On 20 May 2011 the UMC had a very welcome return visit from Sujith Chandy, Department of Clinical Pharmacology & Head of Pharmacy at Christian Medical College, Vellore, India. He came to Sweden as part of his PhD project on antibiotic resistance pursued together with the Division of Global Health/IHCAR at Karolinska Institute, Stockholm. Since his hospital had recently joined the newly-formed Indian pharmacovigilance network (PvPI) he was keen to come back after his visit in 2005. He spent a few hours discussing various practical issues in Indian pharmacovigilance with Sten Olsson.

## New staff

*A number of new permanent staff have joined the UMC recently. We introduce three of them here, with more to come in the next issue.*

"At the age of 21 I decided to move to the most culturally diverse continent in the world – the U.S., where I studied and ended up staying for almost a decade. I graduated with

"Time may be a killer for us all and give us more wrinkles, however, time also makes us smarter. After I got deeply involved in UMC products and business models, I realized that after all the excellent work by UMC's expert staff, over a long period of time, there are so many very useful internal sources available which are absolutely unique in the world and would allow us to do more R&D work. So I am really pleased to work here and to try to make my maximal contributions for UMC."

In his free time, Zhurong likes to play Chinese chess and enjoys travelling to different countries.



*Carin, Zhurong and Berivan*

### Carin Ström

Carin is a new Corporate Secretary, whose responsibilities are mainly supporting UMC Director Marie Lindquist, the Executive Committee and the UMC Board as well as Human Resources and other administration.

She was born and brought up in Uppsala (not so typical for UMC staff) although her family roots are in northern Sweden.

"I was for many years Assistant to a Managing Director in Pharmacia Biosensor AB, one of the subsidiaries of the former Pharmacia group. My last 12 years were spent in the Human Resources administration of the Fresenius Kabi group here in Uppsala."

Outside of the UMC? "We have two children, Josephine (16) and Jacob (13), both adopted from Korea. I also enjoy tours around Sweden with my husband on his Kawasaki 2000 Vulcan."

### Berivan Semyan

"Since childhood I always wanted to explore and have adventures around the world. Different cultures and people have in one way or another been a great passion of mine."

Berivan was born and raised in Sweden by Kurdish parents, and privileged to learn the best of the both worlds – and aside from her native tongue Kurdish, and Swedish, she learned Farsi, Arabic and English along the way.

a degree in Business Communications and worked on Wall Street – where in 2009 I decided to move back home to safe Sweden."

Since, 2010 Berivan has been working as a Web Support Executive in the Sales & Marketing department at the UMC.

### Zhurong Liu

Zhurong is originally from Hunan Province in China, and obtained his BSc degree in pharmacy at the China Pharmaceutical University. In 1998 he received his PhD in pharmacology at Uppsala University, with a thesis investigating the relationship between neurotransmitters in human diseases and animal models and pain.

"I have worked with several pharma companies over the years, including AstraZeneca, SK Biopharm and China. I was focused on discovering new drugs by using animal models to examine efficacy of drugs."

"I joined the UMC in 2009 working in the improvement of content of the WHO Drug Dictionaries. Currently my work has expanded into design and development of new products. By combining various techniques and use of our currently existing sources, it is possible to develop new products used for drug research and development. This is quite a challenge but very interesting and attractive."

## UMC in action

As ever the Swedish spring heralds a burst of physical activity by UMC staff.

Among extra-mural activities over the last quarter, there was a sponsored 'spinning' day where many UMC staff took part to raise money for the relief funds of the Japanese earthquake and tsunami.



*Four exhausted UMC spinners: Mats, Ola, Kristina, Magnus*

As in previous years several staff took part in the nationwide Blodomloppet event held in cities around Sweden on the 31<sup>st</sup> May to raise awareness, in a fun way, of the importance of donating blood. Participants walked or ran around a route south of the city centre through the parks and along the river Fyris. Our fitter colleagues took part, followed afterwards with a picnic.

The annual 'Steg' contest also involved some staff who counted the number of paces they walked or ran every day for a month to see who was travelling furthest on foot.

DATES	TITLE	PLACE	ORGANISER/CONTACT
14-17 August 2011	27 <sup>th</sup> International Conference on Pharmacoepidemiology and Therapeutic Risk Management	Chicago, USA	ISPE www.pharmacoepi.org/meetings/ E-mail: ISPE@paimgmt.com
3-8 September 2011	71 <sup>st</sup> International Congress of FIP – Compromising safety and quality: a risky path	Hyderabad, India	International Pharmaceutical Federation www.fip.org/hyderabad2011/hyderabad_home E-mail: congress@fip.org
7-8 September 2011	Back to Basics in Pharmacovigilance	Southampton, UK	Drug Safety Research Unit Tel: +44 (0)23 8040 8621 www.dsru.org/ E-mail: jan.phillips@dsru.org
12-15 September 2011	Practical Pharmacoepidemiology	London, UK	London School of Hygiene and Tropical Medicine E-mail: krishnan.bhaskaran@lshtm.ac.uk Further details: www.lshtm.ac.uk/prospectus/short/spp.html
19-20 September 2011	Medical approach in diagnosis and management of ADRs	Paris, France	DIA Europe Tel: +41 61 225 5151 E-mail: diaeurope@diaeurope.org
21-22 September 2011	Critical Appraisal of Medical and Scientific Papers: How to read between the lines	Fareham, UK	Drug Safety Research Unit (see above for details)
21-23 September 2011	Advanced pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 730008 www.management-forum.co.uk E-mail: registrations@management-forum.co.uk
29-30 September 2011	XI Jornadas de Farmacovigilancia	Bilbao, Spain	AEMPS www.aemps.es/actividad/actCongresos/2011/FV_XI-jornada_sep11.htm
3-7 October 2011	Excellence in Pharmacovigilance: Clinical trials and post-marketing	Zagreb, Croatia	DIA Europe Tel.: +41 61 225 51 51 Fax: +41 61 225 51 52 Email: diaeurope@diaeurope.org
11-13 October 2011	UMC-A Training course 2011 : Effective communications in pharmacovigilance	Accra, Ghana	UMC Africa Contact: kwaci@hotmail.com
17-20 October 2011	Pharmacovigilance Asia 2011	Singapore	IQPC http://www.pharmacovigilanceasia.com/
19-20 October 2011	Risk Benefit Assessment in Pharmacovigilance	Botley, Southampton	Drug Safety Research Unit (see above for details)
26-28 October 2010	11 <sup>th</sup> ISO <sub>P</sub> Annual Meeting (preceded by training courses on: Basic concepts; Causality assessment; Crisis management – Expecting the worst; Good Pharmacovigilance Practice – Inspection and audits)	Istanbul, Turkey	International Society of Pharmacovigilance www.isop2011.org
31 October 2011	Drugs in the Environment – Ecopharmacovigilance for better health	London, UK	Organizers: Giampaolo Velo (IT) and Giovanni Leonardi (UK) E-mail: gpvelo@sfm.univr.it
9-10 November 2011	Case Narrative Writing for Reporting Adverse Events	Southampton, UK	Drug Safety Research Unit (see above for details)
23-24 November 2011	Pharmacovigilance in Products Subject to Licensing Agreements	London, UK	Drug Safety Research Unit (see above for details)
1-2 December 2011	Advanced Workshop on Pharmacovigilance Planning and Risk Management	Southampton, UK	Drug Safety Research Unit (see above for details)
2 December 2011	Human Medicines Pharmacovigilance Information Day	Dublin, Ireland	Irish Medicines Board Registration forms to kinga.wilczynska@imb.ie or 01-6764971 before 18 November 2011
November 2011 – May 2012	Certificate in Pharmacoepidemiology and Pharmacovigilance	London, UK and distance learning	Registry, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK, Tel: +44 (0)20 7299 4648 Fax: +44 (0)20 7299 4656 E-mail: shortcourses@lshtm.ac.uk



The Uppsala Monitoring Centre (UMC) is a not-for-profit foundation and an independent centre of scientific excellence in the area of pharmacovigilance and patient safety. We provide essential research, reference, data resources and know-how for national pharmacovigilance centres, regulatory agencies, health professionals, researchers and the pharmaceutical industry round the world.

Many of our services and products have been developed as a result of our responsibility – as a World Health Organization Collaborating Centre – for managing the WHO pharmacovigilance network of over 100 countries and the WHO global individual case safety report database, VigiBase™. A core function is the screening and analysis of data with the aim of detecting potential issues of public health importance in relation to the use and safety of medicines. Other services include technical and scientific support to WHO and its member countries, and provision of tools, such as VigiSearch™ and VigiFlow™, for data entry, management, retrieval and analysis.

Our main commercially available products are the family of international WHO Drug Dictionaries, used by most major pharmaceutical companies and CROs.

## Communications information

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

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