

# MUR55



**Pregnancy registers | American travels | Jan Venulet**

**Reporting trends | New training videos**



Marie Lindquist  
Director  
the Uppsala Monitoring  
Centre

*Mrs L, 83 years old, rang me the other day to tell me some good news. At last, she had won what for her has been a real battle.*

*For many years now, she has had to cope with both sensory loss and neural pain as a result of a complication of spinal anaesthesia in connection with a knee operation (she developed a hematoma, which was not diagnosed in time – but that is a separate sad story which I shall not go into here).*

*Eventually she was prescribed gabapentin, which helped against the pain. But one day she told me that she had a problem. She had been given a different product from the pharmacy. When she questioned it, she was told that “this is the same as the one you have had before”. She understood that the active ingredient was indeed the same, and, not wanting to make a fuss, she took the dispensed tablets home. Once home, she found that they were not the same; the new tablets were of a size that made them more or less impossible to swallow. The lack of a shiny coating only made things worse.*

*I recommended her to talk to the pharmacist, explain her problem and ask to get the product she was happy with – it should be possible to override the generic substitution by paying the price difference. She was reluctant to complain and be seen as ‘difficult’, so she stoically did her best to cope until it was time to renew the prescription.*

*This time she got yet another product, which was not quite as bad, so she was feeling a bit happier. At the next renewal however, she was told that the pharmacy had run out of tablets of the right dose, so she was offered a pack of tablets half the strength, and told to take two each time, instead of one. This may seem like a trivial nuisance, and she was rather hesitant to tell me that she now had a problem of a different kind: the two tablets did not fit into the slot in the pillbox she is using - which is an indispensable help in her daily medication management (gabapentin is not the only drug she is taking!).*

*Mrs L’s patience was now running thin, and we agreed that she should try to do something. So, having talked with her doctor and been given a prescription that specifically states that ‘the patient may get the product she is asking for provided that she pays the extra cost’, she was finally able to be supplied with the product that works best for her. Fortunately she can afford the cost, but what do you think would have happened if that had not been the case?*

*This is not a story about adverse drug reactions (Mrs L has had her share of these, too, but that is a price she is prepared to pay for having the benefits of the pain relief), neither is it a political pamphlet against generic substitution. It is simply a real life example of the kind of negative experiences that a patient may encounter in a system that is not primarily focused on the needs of the individual – experiences that may have a serious impact on a person’s trust, adherence and quality of life, and even patient safety – and which deserve to be listened to, and acted upon.*

*The reason I know about what happened to Mrs L is that she is my mother. She has given me her consent to write this text, because she, like so many other patients, wants her story to be told.*

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

FEATURES

4-5  
Vaccines

11  
In memory of Jan Venulet

12-13  
WHO Pregnancy Register project

16  
FIP in India

REGULARS

2  
Director's Message

6-7  
Reporting trends

8-10 ; 14-15  
News from Around the World

16-18  
Conference reports

19  
News from Bredgränd

20  
Training and Publications

21-22  
New staff and visitors

23  
Courses and conferences



Vaccines news

Important meetings at WHO pave the way for progress in vaccine safety

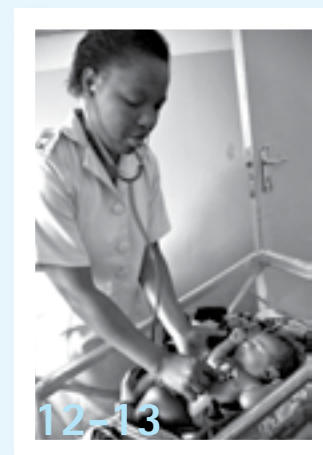


UMC out and about

UMC staff have been meeting colleagues in many parts of the world, including Norway, Costa Rica, Peru

WHO Global Pregnancy Register

A description of an important initiative from WHO towards safer medicines in pregnancy



Conference reports

A round-up of recent international conferences



# Vaccines experts look forward

*Jerry Labadie*

## Global Network

From 22–23 September 2011 the Global Network for Post Marketing Surveillance of Vaccines convened its annual meeting in Château de Penthes, Geneva. Representatives of all 12 member countries (Albania, Brazil, China, India, Iran, Kazakhstan, Mexico, Senegal, Sri Lanka, Tunisia, Uganda and Vietnam) exchanged information on progress and experiences with the implementation of Network activities. Valuable lessons learned, best practices and encouraging examples were shared in a very open and constructive atmosphere.

Topics for Network country presentations and discussions were:

1. how to enhance the detection and reporting of adverse events following immunization (AEFI) at all levels of the health system
2. improving the completeness and quality of AEFI data
3. fostering collaboration between the Expanded Programme on Immunization (EPI) and national regulatory authorities (NRA)
4. positioning a National AEFI Committee within the health system to respond to safety concerns
5. reintroduction of a vaccine following interruption after AEFI
6. how the Institutional Development Plan in the context of the WHO NRA assessment procedure can lead to major improvements in a vaccine pharmacovigilance system.

Institutional Developments Plans are the plans resulting from WHO assessment of a country's national regulatory agency, and



*The Global Network for Post Marketing Surveillance of Vaccines during its 2011 Annual Meeting*

require levels of attainment in several areas (including safety surveillance) in order for a country to be able to apply for the status of WHO pre-qualification of a vaccine.

National work plans of the Network countries for the next year were discussed as an element in defining plans for further development. It was decided that the focus will be on

1. strengthening of data submission and quality
2. causality assessment training, and
3. strengthening of data analysis at country level.

The project funding ends in 2012. With a more long-term perspective the potential contribution of the Network countries to the Global Vaccine Safety Blueprint project was discussed in working groups. Network representatives from India (N. K. Dhamija), Iran (S. Fakhzadeh) and Uganda (H. Nassali) presented the outcomes of these discussions at the 'Global Vaccine Safety Meeting- The Global Vaccine Safety Blueprint'.

## Global Vaccine Safety 'Blueprint'

In this Global Vaccine Safety Meeting – The Global Vaccine Safety Blueprint (26–27 September, Geneva) the findings from a landscape analysis of the vaccine safety infrastructure in low- and middle-income countries were presented to 100 stakeholders (including vaccine manufacturers) in the context of the 'pre-final draft' of the Global Vaccine Safety Blueprint (a blueprint was originally a type of drawing of an engineering design, but has become used in reference to any detailed plan.). The representatives of all 12 Network countries also actively participated in this meeting. In break-out

## Blueprint objectives

**Objective 1:** To strengthen vaccine safety monitoring in all countries

**Objective 2:** To strengthen the ability of countries to evaluate vaccine safety signals

**Objective 3:** To develop vaccine safety communication plans at country level to ensure awareness of vaccine risks and benefits, understand perceptions of risk, and prepare for managing any AEFI and crises promptly

**Objective 4:** To develop internationally harmonized tools and methods for vaccine pharmacovigilance

**Objective 5:** To establish a legal, regulatory and administrative framework to ensure compliance with vaccine pharmacovigilance requirements at national, regional and international levels

**Objective 6:** To strengthen regional and global technical support platforms for a vaccine pharmacovigilance system that meets countries' expressed needs

**Objective 7:** To make international expert scientific advice on vaccine safety issues available to support vaccine safety systems at national, regional and international levels

**Objective 8:** To put in place systems for appropriate interaction between national governments, multilateral agencies, and manufacturers at national, regional and international levels.



*In the main conference room of WHO Geneva, the Global Vaccine Safety Blueprint is discussed*

*continued on page 5*



# New CIOMS report on Vaccine Pharmacovigilance

*Adwoa Bentsi-Enchill, Priya Bahri (on behalf of the Working Group)*



A new report will become available by the end of 2011/early 2012 from the Council for International Organizations of Medical Sciences (CIOMS) which covers the activities and outputs of the CIOMS/WHO Working Group on Vaccine Pharmacovigilance during 2005-2010.

The Working Group brought together, in a unique manner, experts from both industrialized and emerging countries representing vaccine industry, regulatory agencies, national and international public health bodies including WHO and CIOMS, academia and clinical care, contributing from their different perspectives.

## Terms and definitions

The Working Group's report covers general terms and definitions for vaccine safety and discusses the application of such harmonised

tools in vaccine safety surveillance and studies. As well, the report highlights case definitions for adverse events typically reported for vaccines as developed by the Brighton Collaboration (<https://brightoncollaboration.org/public>) and endorsed by this Working Group. The report is addressed to those engaged in vaccine safety data collection and evaluation, and will also make a useful reading for others who want to familiarise themselves with vaccine safety terminology.

## Practical concerns

Agreeing definitions and terms specific to vaccine safety within an international multi-stakeholder forum was the primary objective of the Working Group and the report is very much written keeping in mind those who are at the frontier of data collection and interpretation. For example, the definitions and related criteria for adverse event following immunization (AEFI) and vaccination failure are discussed, with examples to facilitate their practical application. The Working Group also took care to keep the definitions aligned and compatible with the standard terminology already established in pharmacovigilance.

## Wide collaboration

Common case definitions are essential for improved data collection and comparisons between regions and over time, including expected-versus-observed and before-after study designs for investigating whether adverse events are attributable to vaccination. In addition to the Brighton Collaboration, the Working Group benefited further from co-operation with other expert groups in pharmacovigilance; one such example is its collaboration with the CIOMS working group on signal detection reflected by a discussion on signal detection with respect to vaccines in the report.

There is still more to do in the field of vaccine safety, in particular in relation to risk management and communication, and the Working Group members expressed their willingness to contribute to ongoing and future initiatives of WHO and CIOMS in this important area.

## *continued from page 4* *Global Vaccine Safety 'Blueprint'*

sessions all eight objectives of the Blueprint were discussed in terms of challenges, opportunities and solutions, and reported back to the plenary (see box on page 4).

This meeting was part of a step-wise endorsement process in which a draft has previously been presented to the Global Advisory Committee on Vaccine Safety (GACVS). Next, the final draft will be presented to the Strategic Advisory Group of Experts (SAGE) on Immunization. At the end of this process a final Blueprint, broadly endorsed by all stakeholders, will be ready to be presented to potential funders.

## Monitoring Medicines enters final year

*Ennita Nilsson*

Launched in March 2010, this major project funded by the European Commission under its Seventh Framework Programme (FP7) is due to run until February 2013. Five of the scheduled projects have so far been delivered, with the others due for completion in the near future. We were delighted to learn that the EC has confirmed the progress made, and the last sections will be reported over the coming year.

Five countries participating in the collaboration about root cause analysis of medication errors are being supported to present this method at the 34<sup>th</sup> National Centres meeting in Dubrovnik.

Two of the methods developed, Targeted Spontaneous Reporting (TSR) and Cohort Event Monitoring (CEM) will permit two countries to access 30,000 euros to further improve such methods in Africa. Another CEM training course is scheduled for the end of November 2011 in Ukraine.

A web-based tool for patient reporting is currently being developed in collaboration with patient organisations and the UMC production management unit. Training in this tool will be held in March 2012 at Lareb in the Netherlands.

# VigiBase – global reporting trends

Hanna Pedersen & Sara-Lisa Fors, Reporting, Analysis & Country Support

## Cumulative reporting

During 2011, over one million reports have been added to the WHO global ICSR database (VigiBase™), both in terms of new reports submitted and previously submitted reports searchable for the first time. When the latest reporting statistics were presented in UR53 last April, the total of 6 million reports in VigiBase had just been passed, and it seems that it will not be long until the next milestone – 7 million case reports – will be

reached. As of 19<sup>th</sup> of September 2011, the total number of active ICSRs in VigiBase was 6,755,430. The growth of VigiBase since the start of the WHO programme for International Drug Monitoring is presented in Figure 1.

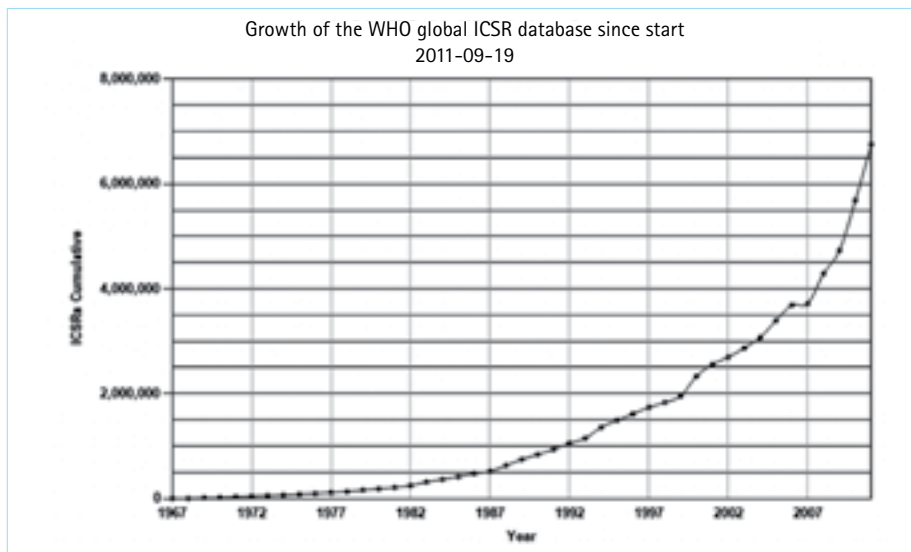
## Reporting rates and country distribution

For many years New Zealand has been the top country in terms of Reporting rate per

million inhabitants and year. However, Singapore has now taken the lead. New Zealand is runner-up for the top position and the USA is currently in third place. Figure 2 shows the top 20 countries in terms of reporting rates per million inhabitants and year, during the last 5 years.

As shown in Figure 3, the proportion of reports in VigiBase from different countries stays mainly the same as before, with the USA accounting for nearly half of the database.

Figure 1. Cumulative number of active ICSRs in VigiBase



## Submission frequency

WHO Programme member countries should submit ICSRs to the UMC on a regular basis, preferably once a month, but at least every quarter. This is important in order to keep VigiBase as complete and as useful as possible for all member countries. More than half of the WHO member countries (61 of 106) have submitted reports four times or more during the last twelve months.

Since the last time the reporting statistics were presented, the proportion of countries sending reports during the last three months has improved, from approximately 57% to 66%. We are glad to report that the proportion of member countries not sending reports to the UMC over the last twelve months has also improved, down from approximately 22% to 18%. See Figure 4 for more details.

Figure 2. Reporting rates (per million inhabitants and year) to the UMC

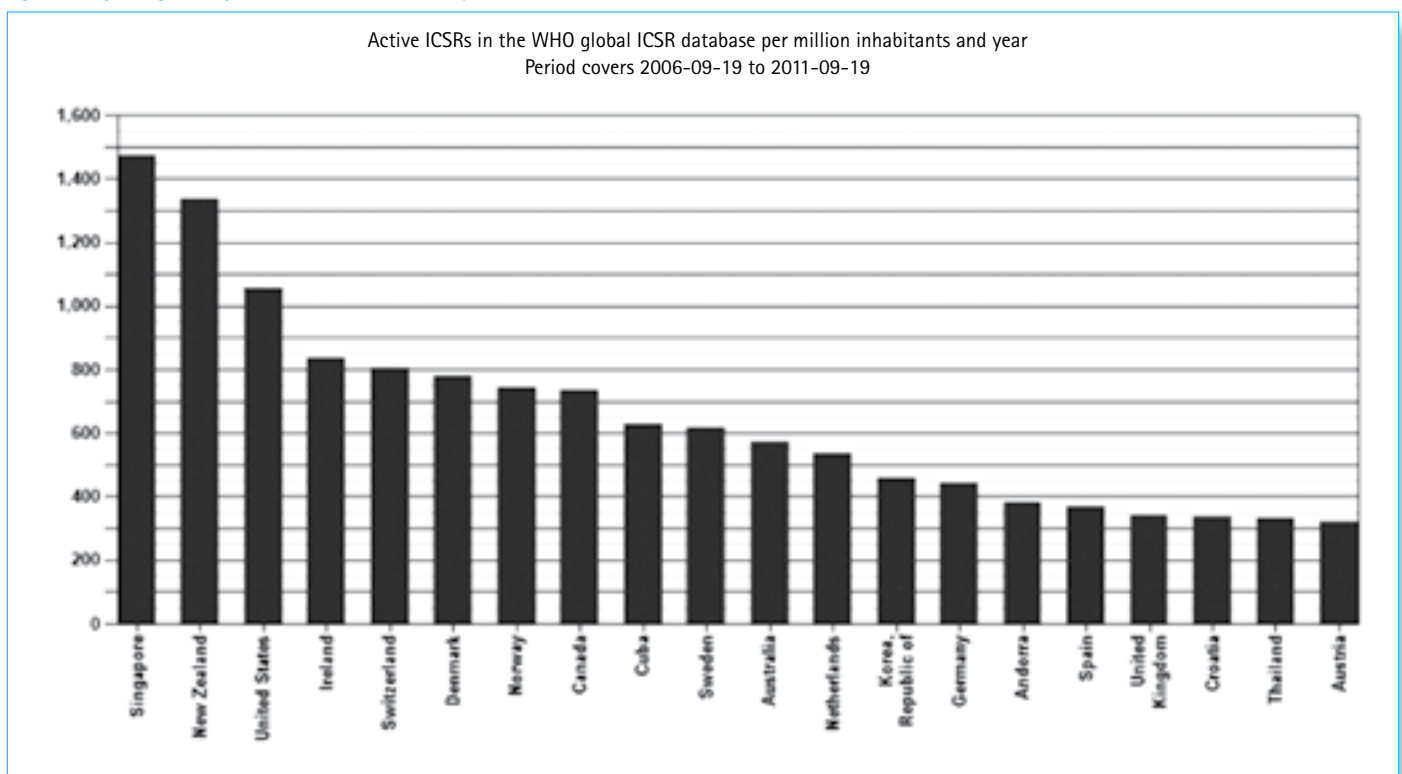


Figure 3. Country distribution of ICSRs in VigiBase as of September 2011

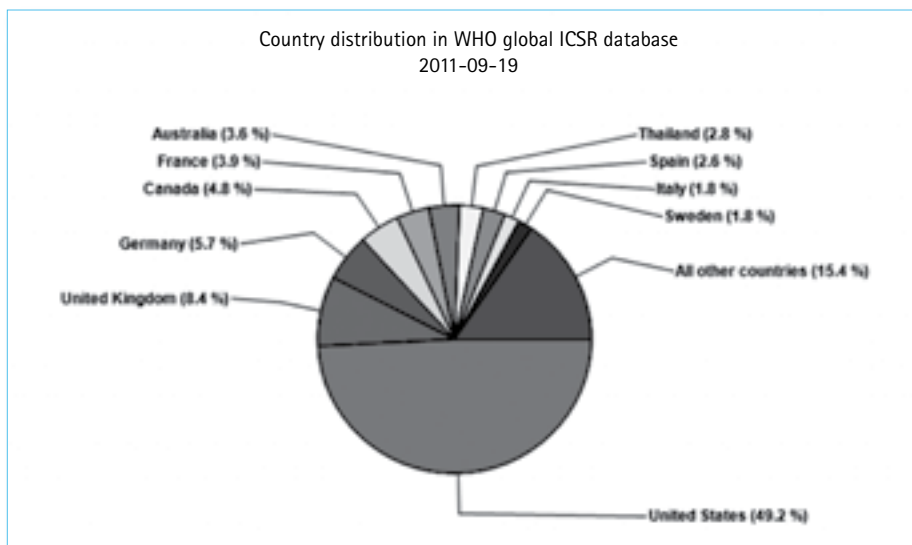
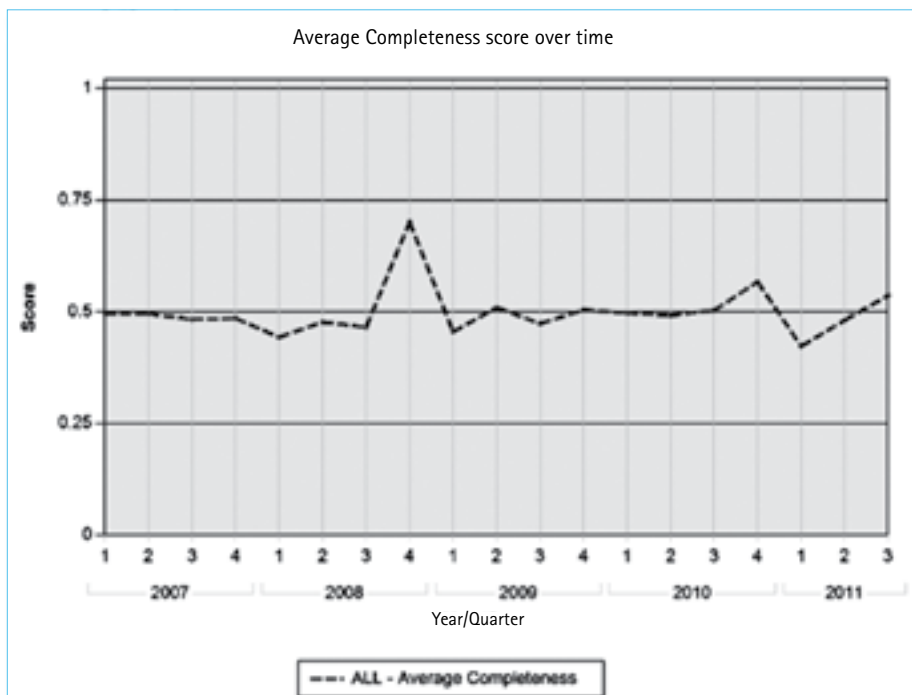


Figure 5. Average completeness score of all ICSRs in VigiBase.



Graph of the average completeness score over time for all ICSRs in selected countries. The dotted line represents the average completeness for all countries.

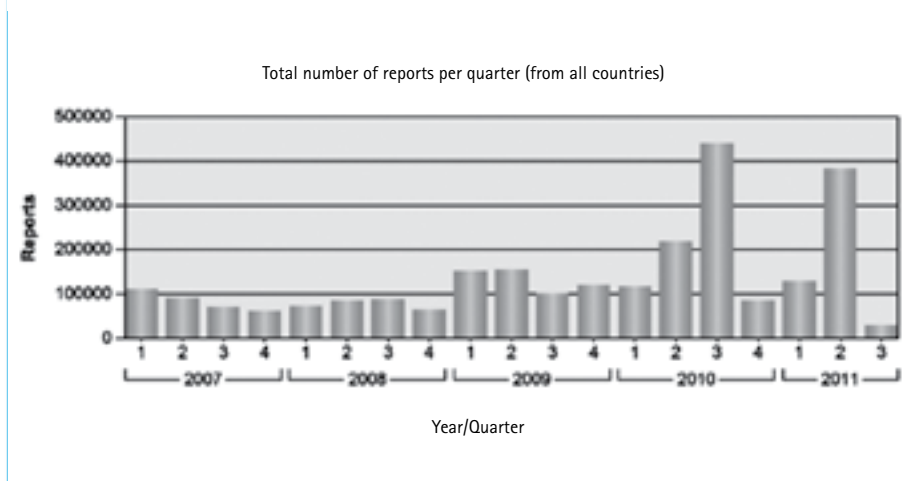
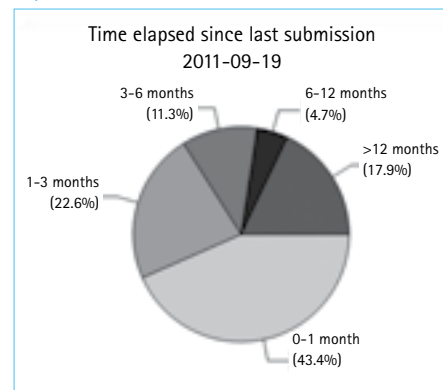


Figure 4. Time elapsed since last submission (proportion of countries as percentage) as of September 2011



### Reporting format

The current number of member countries is 106. As of September 2011, 77 out of 106 member countries were reporting in the recommended ICH-E2B format, of which 45 were using VigiFlow™ as their Individual Case Safety Reports (ICSRs) management system. India and the Philippines recently switched from the old WHO-format (INTDIS) to VigiFlow, and the two new member countries Mali and Benin are also using VigiFlow.

### Average completeness score in VigiBase

During the past year the UMC has started to put more emphasis on the quality of reports in the database. One of the quality measures is to see to what extent the reports are filled in, the so-called completeness score (see Documentation grading – how complete are the reports, in UR54). An average score of all the reports over time is shown in Figure 5. Since the score is an average of all the reports in VigiBase, countries that submit many reports every quarter will have a very large impact on the average score compared to other countries.

# National centre visits continue to Norway

*Cecilia Biriell and Jeanette Johansson*

UMC staff visits to national pharmacovigilance centres in Europe, which have turned out to be very useful for better co-operation between those centres and the UMC, are continuing. Latest was a two-day visit by Jeanette Johansson, from the Analysis section and Cecilia Biriell from the Country Support section to Statens Legemiddelverk (the Norwegian Medicines Agency – NOMA) situated just outside Oslo.

We were welcomed on our first day at NOMA by Jan Petter Akselsen, Head of the Department of Drug Evaluation, where pharmacovigilance is organisationally placed, Ingebjörg Buajordet, Pernille Harg and Hilde Samdal. It was really good to meet Ingebjörg again, as she has been working as head of pharmacovigilance for many years, but now mainly spends her time on European collaboration. Pernille has been representing the Norwegian centre at the annual WHO meetings for the last few years. Pernille is responsible for reporting from health professionals and functions as the main UMC contact person. Hilde is responsible for the on-going patient reporting pilot project.

responsible for drug information in their regions. Although compared to other countries Norway has a reasonable reporting rate, NOMA staff do not think it is satisfactory. Jan Petter Akselsen thought it would not improve until healthcare professionals can report automatically through a 'one-click' function in patient record systems.

## Patients report

Patient reporting is made on-line through NOMA's website, so far as a pilot project, but the plan is that regional centres will also take over patient reporting when the project has been evaluated.

We presented the UMC and its activities, how to use VigiSearch and VigiMine, as well as UMC's work in finding new ADR signals, to around 50 people of the NOMA staff at a so-called 'canteen seminar'. We also discussed how NOMA best can use VigiSearch and VigiMine in their work and make best use of signals presented by the UMC.

The first day finished at an excellent Vietnamese restaurant Xich Lo. We didn't get the chance to taste the traditional Norwegian

things touched upon how signals from UMC can possibly be better used in the European pharmacovigilance work at EMA and in the CPMP.



*Food for pharmacovigilance – Norwegian specialties at NOMA*

This visit will soon be followed by one to the national centre AGES in Vienna, Austria – which we will report in the next UR.



*Our hosts at NOMA; Hilde Samdal, Jan Petter Akselsen, Ingebjörg Buajordet and Pernille Harg*

## Health care structure

In his introduction Jan Petter Akselsen pointed out that the equal right to healthcare, regardless of where people live in the country (which stretches from Tromsø above the arctic circle and further north, to Oslo in the south), is a strong principle in Norway and hospitals are therefore run by the state, not regional governments. Adverse reaction reporting from healthcare professionals is mainly made to the four regional centres (RELIS – Regional Medicine Information Centre) at university hospitals which also are

'Får i kål' (Sheep in cabbage) which was served in the NOMA canteen that day.

On the second day we visited the regional centre RELIS South-East at the Ullevål University Hospital. The RELIS staff were very interested in the on-going development of new search concepts in VigiBase (called VigiLyze) and were willing to become a test centre for the new functionalities.

Our visit finished off with a summary discussion at NOMA where we among other



## UMC Course 2012

Yes, that's right, the UMC pharmacovigilance course will be held annually from now on, so there will be a course next year as well. The preliminary dates have been set as 21 May - 1 June. The course announcement and application form will be sent to all National Centres in October/November and will also be available for everyone on the UMC website.

If you have any questions about the course, please e-mail the new course administrator Marie Wallin ([marie.wallin@who-umc.org](mailto:marie.wallin@who-umc.org)) or the course manager Anna Hegerius ([anna.hegerius@who-umc.org](mailto:anna.hegerius@who-umc.org)).

## Let's communicate!

The October edition of *Drug Safety* contains a report of a workshop held at the 2010 International Society of Pharmacovigilance meeting in Ghana. An interactive debate discussed the challenge of public communication on safety concerns over medicines and advice on how to prevent medicine-induced patient harm.

Around 30 participants came together and presented views from their various perspectives: community and hospital pharmacy, academia, pharmacovigilance centres and regulatory agencies, as well as international bodies.

Although much is known in theory about good communication, how to achieve this in practice is more problematic. This debate defined 'reciprocity' as the starting point: "an exchange of information based on mutual respect and shared interest".

The workshop concluded with a vision "that those working in drug safety approach communication as passionate advocates, creating campaigns on major topics concerning safe and effective use of medicines, and using various media and original interventions". An essential reminder of the central importance of this topic in patient safety.

Bahri, Priya; Mol, Peter G.M; Théophile, Hélène; Edwards, I. Ralph; Hugman, Bruce P.J. *Communication in Drug Safety: A Report from an Interactive Debate Held at the 10<sup>th</sup> Annual Meeting of the International Society of Pharmacovigilance (ISoP), 2010. Drug Safety, 1 October 2011 - Volume 34 - Issue 10 - pp 881-882.*

## UMC Research Conference

24-25 May 2012 – Uppsala, Sweden

### Causality Assessment in an Evolving Pharmacovigilance Landscape

Uppsala Congress Centre will be the venue for an Uppsala Monitoring Centre research conference on causality assessment. International experts in pharmacovigilance and pharmacoepidemiology will join researchers from the UMC in an open research meeting to discuss the current challenges and future directions of causality assessment.

Assessing and interpreting the strength of evidence in favour of a causal association between one or more drugs and adverse reactions is fundamental and affects the future of patients and drugs alike.

Professionals making these decisions on a daily basis face intriguing, sometimes philosophical challenges when dealing with the range of hypotheses and evidence that could explain any observed phenomenon. The outcomes of decisions affects the lives of patients and the viability of drugs.

The UMC's Research Conference 2012 will address these topics, dissect case reports, consider observational studies and view randomized trial data in order to debate what the evidence can and cannot tell us.

Day 1 'Principles of causality assessment', will cover

Philosophy of science

Causality assessment using case reports and on the bedside

Controlled clinical trials and cohort event monitoring

Assessing causality from observational studies

Is it possible to automate causality assessment within the OMOP model?

Benefit-risk

Day 2 'Causality assessment in practice' will present the issue from a variety of standpoints: patient, industry, regulatory, insurance, legal, media.

To register your interest please e-mail [conference2012@who-umc.org](mailto:conference2012@who-umc.org)



*The congress and concert centre in Uppsala*

# Advanced briefing in Geneva

*Lovisa Sällstedt and Sara-Lisa Fors*

On 12-16 September 2011 the annual Advanced Technical Briefing Seminar on Quality Assurance and Safety of Medicines was organized by WHO Headquarters in Geneva, Switzerland.

from the Quality Assurance and Safety of Medicines (QSM) unit presented the different areas of work within the QSM Technical Programmes. Topics covered included Medicines Regulations, WHO Standards for

## Pharmacovigilance at the fore

One full day was dedicated to pharmacovigilance and the WHO Programme for International Drug Monitoring. The sessions were led by Dr Shanthi Pal, head of the WHO Pharmacovigilance Programme, Dr Pia Caduff-Janosa from Swissmedic (Swiss Agency for Therapeutic Products) and Mr Sten Olsson from the UMC. Topics such as the need for pharmacovigilance, methodologies and tools in pharmacovigilance as well as the importance of communication were discussed. Related to the safety programme, the Anatomical Therapeutic Chemical (ATC) classification and the Defined Daily Dose (DDD) for medicines were presented by Mrs Hanne Strøm from the WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway.

## Wide participation

The Technical Briefing Seminar is open to anyone interested in the areas of work covered by QSM. This year the participants represented non-governmental organizations, ministries of health, national regulatory authorities, universities as well as local WHO offices, from all over the world. The UMC was represented by Lovisa Sällstedt and Sara-Lisa Fors from the Pharmacovigilance Services Department.



*Participants at the 2011 Advanced Technical Briefing in Geneva*

The aim of the seminar was to increase the knowledge of quality assurance and safety of medicines work at WHO and to promote collaboration between WHO and its stakeholders within the field. Representatives

Quality Assurance of Pharmaceuticals, Prequalification of Medicines and Quality Assurance and Safety of Blood Products.

## WHO Programme news

*Sten Olsson*

### Mali

Two more African countries have become full members of the WHO Programme for International Drug Monitoring. At the end of July Mali became the 105<sup>th</sup> member country of the Programme. The principal contact is :

Dr Samba Sow  
Director General  
Centre National de Pharmacovigilance, Mali  
BP: 251, CNAM/CVD-Mali, Ex-Institut  
Marchoux, Djikoronipara  
00223 Bamako  
République de Mali

### Benin

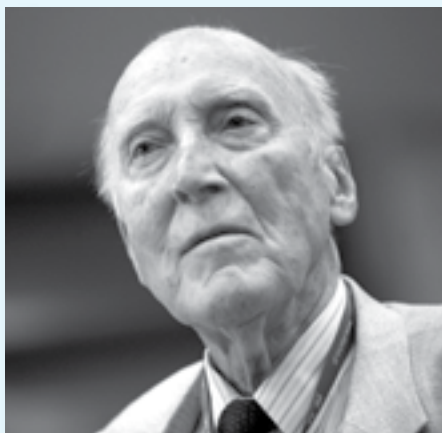
The national pharmacovigilance centre of Benin applied for membership in the WHO Programme in June 2007. In mid-August 2011 it had, through VigiFlow, submitted the first batch of adverse drug reaction case reports to VigiBase. The head of the national pharmacovigilance centre is:

Dr Hounkpevi D Benoît  
Direction des Pharmacies et du Médicament  
Ministère de la Santé du Benin  
01 BP, 2048  
Cotonou  
Benin  
Tel +229 21330882  
Fax +229 21330882  
e-mail: dotoubenoit@yahoo.fr; dpmms@  
yahoo.fr

Since working relationships have now been established between the UMC and the national centre in Benin the country is to be admitted as the 106<sup>th</sup> full member of the WHO Programme for International Drug Monitoring.

As this edition of Uppsala Reports goes to press we are all getting ready to go to Dubrovnik for our annual WHO Programme meeting. We hope to see more progress in developing and sustaining national pharmacovigilance programmes during that week.

# Jan Venulet 1921–2011



*Professor Jan Venulet is considered by many to be the father of the WHO Programme for International Drug Monitoring.*

Jan Venulet was born on 27 May 1921 and spent his childhood in Łódź and Warsaw. His father Franciszek Venulet (1878–1967) was an enlightened and progressive professor of medicine at Warsaw University.

## Studies and early career

Venulet started his medical studies in the underground university during the German occupation of Poland, when he was also involved in the resistance movement *Armia Krajowa* and took part in the Warsaw Uprising.

He continued his studies at the Jagiellonian University in Kraków, where he worked as a junior and senior assistant in the Department of Pharmacology and completed a PhD.

In the 1950s Jan Venulet was an Assistant Professor in Lublin in eastern Poland, then served as director of the Institute of Tuberculosis and Department of Pharmacology, at the Drug Institute in Warsaw from 1953–1975.

## International work

There followed several scientific attachments in Budapest, London and Basel, and three years as professor in Damascus, Syria. He joined WHO as professor of pharmacology working in Rabat, Morocco, then Bangkok, Thailand. In 1964 he wrote the first book in Polish about adverse drug reactions. While in Bangkok as part of the WHO programme for strengthening medical education, he was approached by WHO Headquarters, and asked to organize a new programme for drug monitoring.

## WHO Programme

Accepting the WHO offer, he was involved in the pilot research phase of the monitoring programme, in Alexandria, Virginia, USA developing ADR terminology and the Drug Reference List. From 1968 Jan Venulet was

Senior Project Officer, and responsible for the development of all aspects of the project with a team of professional officers. Signalling 'lists' with the intention of automatically drawing attention to certain predetermined conditions were developed. Signals were analysed by the group or by experts at national centres and circulated as 'Drug Comments' to the centres. Regulatory actions were taken on several occasions. The project was positively evaluated by the World Health Assembly, and in 1970 (following full Programme meetings in Alexandria in 1968 and Geneva in 1969) transferred to Geneva to become an ongoing WHO activity.

Writing about the early years of the WHO Programme, Venulet commented on how he found himself, as a physician specialized in experimental pharmacology, used to clear hypotheses, standardized conditions, statistical evaluation of results, suddenly working in a field where the norm was retrospective analysis of "frequently incomplete and poorly documented case reports of suspicions, sent in by health professionals from different countries" – with an "unknown number of unknown variables".

Jan Venulet was also involved in pioneering efforts to analyse the cost of adverse reactions (WHO Chronicle, 1975). In 1974 he published an article<sup>2</sup> in which the two words 'epidemiological pharmacology' (pharmacology-epidemiology) were used together for the first time. Two more papers on the topic were published by him in 1978 and 1999. He suggested that epidemiological pharmacology was a stage in the evolution of pharmacology from materia medica through experimental, clinical and epidemiological pharmacology to social pharmacology.

## After WHO

Withdrawal of a Polish government agreement meant his departure from WHO in 1975. He became Visiting Professor of Clinical Pharmacology at Geneva University, and later head of intensive surveillance with Ciba-Geigy.

In Uppsala Reports in 2003 (UR22), he expressed the view that the assessment of whether a given drug is the cause of an adverse event remained the most controversial issue in drug safety. While at Ciba-Geigy both unstructured assessments and standardized assessments were undertaken to ensure that subjective and objective views balanced in the overall assessment.<sup>3</sup>

After retiring he lived near Geneva but continued with consulting activities, mainly as senior adviser with CIOMS. Professor Venulet

was the author of around 250 scientific papers, (mainly related to pharmacology), but also thoughtful articles on ethics and philosophy. He died in Geneva on 21 August.

In his professional life Jan Venulet travelled full circle from research and teaching, through regulatory work, WHO, and pharmaceutical industry. He also went from experimental pharmacology to clinical pharmacology and the application of epidemiological methods. His vital contribution to pharmacovigilance in its formative stages was powerful and distinguished.

## Ronald Meyboom reflects

As the man who had in the early 1970s coined the phrase 'social pharmacology', Professor Jan Venulet was a scientist with a vision. Already, in the early days of pharmacovigilance, he had fully grasped the dominant role that drug safety was going to play in modern pharmacotherapy; that safety often determines the balance of benefit and harm, that safety is often the basis of patient confidence and adherence, and that safety is the Achilles' heel of drug regulation and drug innovation.

His broad clinical and pharmacological background, together with his personal interests and skills, meant Jan was the ideal person to put the novel international pharmacovigilance system on track. In this respect the premature termination of the original WHO centre in Geneva was an injustice to Jan and his team. In the spring of 1974 at the meeting of National Centre representatives, his team presented, at a time when computers were generally in a primordial phase of development, results of quantitative signal assessment already operational at the WHO centre.

An elegant gentleman, around fifty at the time of the founding of the WHO Programme, and an eminent scientist, Jan was a born teacher who showed great empathy for young colleagues and newcomers to this unusual profession, and an international circle of befriended colleagues developed who took his messages with them; friends who for the rest of their lives will remember him as the modest giant that he was and will cherish his memory.

1 WHO's International Drug Monitoring – The Formative Years, 1968–1975: Preparatory, Pilot and Early Operational Phases. Venulet J, Helling-Borda, M. *Drug Safety*, 2010, 33(7):e1–e23.

2 From experimental to social pharmacology – Natural history of pharmacology. *International Journal of Clinical Pharmacology* 1974; 10: 203–205.

3 The algorithm is summarized in 'Assessing cause and effect relationships of adverse drug reaction reports'. In: *Monitoring for Drug Safety*, 2nd edition, ed. Inman, WHW. Lancaster, MTP Press, 1986.

Photo credit : Paweł Pawłowski/WNP.PL



# WHO Global Pregnancy Register

## Overview

In low-income countries, the frequency and nature of congenital anomalies in newborns are poorly understood. Furthermore, the contribution of birth defects to fetal and neonatal mortality in these regions is unknown. Some congenital anomalies, such as neural tube defects (NTDs), are preventable with good pre-conceptional and antenatal care and postnatal counselling, and treatments that could profoundly improve health and quality of life are available for NTDs and many other anomalies. A deeper understanding of the need for these interventions would lead to wider access to them.



To meet the challenge of Millennium Development Goals (MDGs) 3, 4 and 5, which seek to improve maternal and child health and combat HIV/AIDS, life-saving treatments such as antimalarials and antiretrovirals are being deployed on a large scale in countries where the prevalence of birth defects is ill defined. The safety of some of these medicines in pregnancy is poorly understood and, in certain cases, animal studies have raised concerns about the potential risk of harm to the fetus (e.g the artemisinins that are prescribed for malaria). Lack of information about drug safety in pregnancy could undermine public confidence in life-

saving therapies and the access of these otherwise safe and effective treatments to patients that are particularly vulnerable to these diseases. Similar situations are likely to arise as newer therapies targeted towards neglected diseases continue to be introduced into these markets.

### United Nations Millennium Development Goals (MDGs) 3, 4 and 5

#### Goal 3

Promote Gender Equality and Empower Women

#### Goal 4

Reduce Child Mortality

#### Goal 5

Improve Maternal Health

<http://www.un.org/millenniumgoals/>

As a result of these concerns, the World Health Organization has initiated a Pregnancy Registry project aimed at assessing the safety of medicines during pregnancy and establishing the frequency of congenital anomalies in low-income countries. To ensure that the project is sustainable and optimises benefit to the pregnant women at the surveillance facilities, the registry will provide ongoing support and feedback to study staff and policy-makers. This support is aimed at all those who are working towards improving the supply and demand for maternal and newborn care in these communities and addressing critical public health questions around the risk factors for adverse pregnancy outcomes.

## What is a pregnancy register?

A pregnancy register is a prospective observational study that collects information on women who take medicines and vaccines during pregnancy. In order to reduce the risk of bias, the health of the fetus should be unknown at the time of enrolment, and the health data obtained from women taking the medicine under study should be compared with data on babies of women who did not take the medicine during pregnancy.

## Design and methods

The design adopted by WHO is to select countries and sentinel surveillance sites where the risk of exposure to antimalarial and antiretroviral medicines during

pregnancy is likely to be high based on the prevalence of the diseases in these areas. Women are recruited (regardless of drug exposure) during their first antenatal visit and followed up throughout the course of pregnancy until they deliver. A detailed medical and drug history is obtained from these women during all antenatal visits. The outcome of the pregnancy is then documented along with the health of the mother and child and the presence of birth defects in the baby. Newborns with birth defects are referred to a neonatologist for confirmation and management and reviewed by an international birth defects panel.

## WHO approach to a sustainable pregnancy register

The Pregnancy Registry project arose as a partnership between various WHO departments, which all recognised the need for developing a single registry that could address the need for obtaining robust data on pregnancy exposures and maternal and neonatal outcomes while ensuring that the Registry can contribute to improving the quality of care provided at sentinel sites.

In each of the countries, the success of the Registry relies on a collaborative approach that engages ministries of health, researchers, NGOs, and health facilities. The Registry is collaborating with other projects and developing interventions that attempt





to address the maternal and neonatal health challenges within the local context. Addressing these challenges through innovative interventions are likely to have broader benefit to maternal and child health and the health system than just meeting the primary objectives of the study and improve the sustainability and feasibility of a surveillance system for assessing the teratogenic potential of medicines.

Fundamental to the project is that all national pregnancy registries will be under the stewardship of the country in which it is housed. Although data on birth defects will be pooled across countries to facilitate assessment of risks during pregnancy, each national database will be housed and managed at a national level.

### Assessing feasibility and acceptance of register: a pilot project

In 2008 a pilot project was initiated to assess the feasibility of a pregnancy registry in rural and urban settings where facilities are understaffed and underresourced, exposure to medicines is poorly understood, and most women prefer to deliver at home. The pilot project is being conducted in Brazil, Ghana, Kenya, Tanzania, and Uganda.

Prior to initiation of the project in these countries, scoping visits were conducted to assess whether health policy-makers agreed

on the need for a pregnancy registry and would support a sentinel surveillance system in their country. Once official support for these projects was obtained and ethics review completed, a mixed methods pilot study designed to assess and evolve case record forms and study procedures was implemented and is ongoing. A flexible training curriculum, educational materials (including a training DVD), monitoring and assessment tools and case record forms are being developed. Problems and challenges are addressed in consultation with an international team of investigators. A periodic newsletter circulated to study staff provides continuous feedback and suggestions on how particular challenges can be addressed while providing a platform for study staff across countries to learn from each other.

Using qualitative methods women recruited in the registry and mothers in the community are being consulted about medications they take during pregnancy, perceptions around birth defects and their attitudes towards a pregnancy registry. Health staff are encouraged to provide constructive feedback on the case record forms, registry procedures and impact of the registry on their existing workload and quality of care they provide.

### Project partners

#### Managing partner

WHO Tropical Diseases Research, in collaboration with WHO Making Pregnancy Safer, WHO HIV/AIDS Program, WHO Global Malaria Programme, WHO Quality and Safety of Medicines Program, WHO country offices – Ghana, Uganda, Kenya and Tanzania.

#### Associated partners

- Ministerial support for the development of a prospective pregnancy registry has been obtained from the pilot countries
- Malaria in Pregnancy Consortium ([www.mip-consortium.org/](http://www.mip-consortium.org/))
- School of Medicine, Moi University, Kenya
- National Institute of Medical Research, Tanzania
- Ghana School of Public Health, Ghana University, Ghana
- Makerere University, Uganda
- Universidade Federal do Rio Grande do Sul, Brazil



- Division of Clinical Pharmacology, Eduardo Mondlane University, Mozambique
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*This article is based on the July 2011 issue of the Project Brief.*

*Photo credit – Ms Mackensie Yore*



## Costa Rica course

*Elki Sollenbring*

Since I was going to be visiting Costa Rica, the Drug Information Centre (CIMED) of the Costa Rica University invited me to run a basic pharmacovigilance training course for

and universities attending. I made nine different presentations, but equally valuable were the exchanges of knowledge with a very keen group of people. The content of

training, which I could see it was exciting for the participants to try.



*Students and lecturers outside the main college building in San José*

health professionals. The course took place on 17-19 August in the College of Pharmacists in San José. It was a three-day course with around 25 professionals from different hospitals, pharmacies, industries

the course included topics from the WHO Programme for International Drug Monitoring, the need of pharmacovigilance, signal detection, the safety monitoring of traditional medicines, as well as VigiFlow



*The course students working during the San José course*

My impression is that the knowledge about pharmacovigilance is still in its early stages in this region but they are very enthusiastic and want to learn more. As a Costa Rican it is important to participate in this kind of activity since I would like my country to be as active as other countries in Latin America in this area.

I thank the staff of the Drug Information Centre, especially Dr Victoria Hall Ramirez (Head of CIMED), for the great job they did and for the amazing hospitality they gave me during my days in San José.

## Pharmacovigilance in Peru

*Elki Sollenbring*

Silvia Alvarez Martel, head of the national pharmacovigilance centre in Peru, invited the UMC to participate in an international pharmacovigilance course that was organized by Pan American Health Organization (PAHO) and the Dirección general de Medicamentos, Insumos y Drogas (DIGEMID) and held in Lima, on August 22-24.

Three hundred people attended the course. Half of the group came from the pharmaceutical industry and the rest from the regulatory authorities, universities, hospitals, with a mix of different professionals, doctors, pharmacists. Different countries were represented: Colombia, Chile, Ecuador, Bolivia, Paraguay, Brazil and of course Peru.

working at the Pan American Health Organization's headquarters), Yu-Xiao Yang from the University of Pennsylvania, USA, Amarilys Vega from FDA via a video-link, and Ernesto Vera, Inspector from AEMPS.



*Murillo Freitas, PAHO, Rosa Amelia Villar Lopez, from PAHO's office in Peru, Ernesto Vera, AEMPS, Elki Sollenbring of the UMC, Silvia Alvarez, Head of Peru's national centre, Mariano Madurga, AEMPS*

It was a four-day intensive course where all speakers had the opportunity to talk about different parts of pharmacovigilance. I presented the WHO Programme for pharmacovigilance and the other speakers ranged from signal detection, drug safety regulation, to inspections of the pharmaceutical industry. The audience was very motivated and had many questions. The speakers included people with wide experience in pharmacovigilance: Mariano Madurga from the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Claudia Vacca from the National University of Colombia, Murillo Freitas, a member of [ACSoMP], who presented his experiences as head of the Agencia Nacional de Vigilancia Sanitaria in Brazil (he is now

I took the opportunity to meet people from Ecuador, Bolivia and Paraguay; these countries are not yet members of the WHO Programme. They clearly wanted information on how to become a member. Good news is that Bolivia and Paraguay now have a national pharmacovigilance centre; we look forward to seeing them as full members.

I also took the opportunity to visit the Peruvian national centre (DIGEMID) and make a presentation for the workers of the centre. It was excellent to see where and how they work.

As usual, the visit was an invaluable time to share experiences with all these wonderful people and to know more about this beautiful country. Thank you to the organizers for the warm hospitality extended to all who attended.



## Seven countries in Guatemala

*Mariano Madurga*

A new training course on pharmacovigilance was held in Antigua Guatemala from 1<sup>st</sup> to 5<sup>th</sup> August 2011. The course was supported by and held in the Training Centre (Centro de Formación) of the Spanish International Agency for Co-operation for Development (AECID) in Guatemala. Mariano Madurga (director) and Ramón Palop from the Spanish Medicines Agency (AEMPS), Julio Valdés (SICA, System Integration of Central America) and Juana Mejía and José Luis Castro from the Pan American Health Organization (PAHO/OPS) were the teachers and course leaders.

The healthcare professionals participating came from seven ministries of public health and social security administrations (Costa Rica, Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, Panama) but had one objective: to consolidate the regional programme of pharmacovigilance of Centro-America y Dominican Republic into the SICA activities, using the Spanish AEMPS experience over the last 25 years.

In the beautiful setting of Antigua, the 20 professionals (medical doctors and pharmacists) from the seven countries had a great opportunity for concentrated training in spontaneous reporting, pharmacovigilance systems, pharmacovigilance of vaccines and



*Planning for collaboration - participants on the course in Antigua Guatemala*

biotechnological products, risk assessment of medicines, methods of drug utilization research, lack of efficacy and medication errors.

Practical cases were discussed during workshops about individual causality assessment, qualitative and quantitative analysis of signal risk management, planning a new national pharmacovigilance system,

and taking regulatory decisions. Finally, development support for a regional pharmacovigilance programme was planned, co-ordinated by the Panama centre and the expertise of AEMPS pharmacovigilance staff. This work was based on an intranet system (e-Room) offered by AEMPS to connect pharmacovigilance professionals from different countries. Some first steps to a collaborative programme in Central America.

## Workshop in Quito

*Mariano Madurga*

A workshop 'Pharmacovigilance in the Public Health Network' was held from 17<sup>th</sup> to August 19<sup>th</sup> in Quito, Ecuador. The event was promoted by the Ministry of Public Health (MSP) of Ecuador, through the Department of Control and Improvement of Health Surveillance. About 80 attended professionals responsible for the public health network in the country attended. The Deputy Minister of Health, Dr Nicholas Jara, stressed the relevance of the event, as on the 16<sup>th</sup> he had just signed the new law on the operation of the Ecuadorian System of Pharmacovigilance. This represents a historic shift in generating health information in order to ascertain what is happening with the use of drugs in Ecuador. A press release was issued on the [www.elciudadano.gov.ec/](http://www.elciudadano.gov.ec/) website: <http://tinyurl.com/6j5roq>

At the workshop Mariano Madurga (AEMPS) introduced pharmacovigilance as an assurance for the rational use of drugs, along

with other presentations on pharmacovigilance as a professional responsibility, analysis and risk management, risk identification, ineffectiveness or therapeutic failures, pharmacovigilance methodology in hospitals and primary care, and characteristics of the pharmacovigilance databases (WHO-DD dictionaries, MedDRA and WHO-ART, codifying DCI / INN and ATC, etc). A workshop on coding and evaluation of ADRs was much appreciated. Other presentations were from Consuelo Meneses on the results of CIATOX Antipoison Centre and its handling of ADR reports; on AEFI from the Expanded Program on Immunizations (EPI), and Greta Munoz about active pharmacovigilance and risk management with antibiotics.

All this was related to the new 'Rules of Operation of the National Pharmacovigilance' presented by Fabiola Gallegos, of the Department of Control and Improvement of Health Surveillance, MSP. Now the law



*Participants face-to-face in a workshop on codification in Quito*

needs to be developed and implemented: we wish all success for this purpose for the health of the Ecuadorian people.

The text of the regulation: <http://www.msp.gov.ec/index.php/Farmacovigilancia/>

# FIP Fanfare for Pharmacy

*Bruce Hugman reports from Hyderabad, India*

The seventy-first annual world congress of FIP (International Pharmaceutical Federation/Fédération Internationale Pharmaceutique) was a memorable affair, attracting more than two thousand participants from around ninety countries. It was this reporter's first FIP meeting, and he was deeply impressed by the extraordinary quality of all the complex arrangements, the wide range of beautifully produced materials, and the distinction of many of the sessions and guest speakers: this is a very serious, highly professional organisation!



*The director of the Indian pharmacovigilance centre, G.N. Singh (2nd from right), explaining the structure of the Indian pharmacovigilance system (PvPI) to Sten Olsson, Shanthi Pal and Paul Lalvani at the booth of the Indian Pharmacopoeia Commission (IPC)*

## Endorsement from the very top

The meeting was opened by the President of India, Shrimati Pratibha Devisingh Patil, who delivered a number of highly pertinent messages about pharmaceutical science, pharmacovigilance and patient safety, and about India's current expanding regulatory and industrial activities in the field. It was a speech for which she had been well briefed (see box for extracts).

With public endorsement at such a level, the prospects for the profession in India seem bright, not least for pharmacovigilance (after such a chequered history in recent years), as the national system is placed under the aegis of the Indian Pharmacopoeia Commission (IPC), supervising the 42 regional centres<sup>1</sup>.

## Wide scope of interests

The theme of the conference was: 'Compromising safety and quality: a risky path' and many of the seventy or so sessions

examined new thinking and processes for improving safety and reducing harm - including sessions on counterfeit medicines, medication errors, generics, vulnerable populations, pharmacologistics and much more.

A major, recurring theme was the development of the pharmacy profession to meet the economic, social and healthcare challenges of the modern era: how can pharmacy embrace the role of healthcare provision within an integrated service delivery system, and play a front-line role in counselling patients and their communities and protecting them from harm? Many examples of new practice were mentioned, including the provision of a range of monitoring services, patient support groups, outreach with schools and community groups, maintaining patient records and productive collaborations with physicians and hospitals.

Important new developments in educational technology were presented (the virtual pharmacy; animated online tableting; open access repositories of pharmacy literature and resources, for example) - along with sound evidence that modern methods, used purposefully and selectively, enhance student learning and can significantly reduce costs.

## Pharmacovigilance in the spotlight

Programmes occupying a full day and a half were focussed on pharmacovigilance, with UMC (Sten Olsson and Alex Doodoo), and WHO (Shanthi Pal) taking prominent roles in them.



*The Charminar: built by Sultan Muhammad Quli Qutb Shah, the 5th ruler of the Qutb Shahi dynasty in 1591 AD, to celebrate the eradication of plague in the then capital city.*

*Photo: Didier Tais; Wikipedia Commons*

A lively session on mass communication skills for pharmacists drew a large crowd, and UMC again played a major role in spreading the message about the critical importance of development and energy in this area (Bruce Hugman and Alex Doodoo).

## Major worldwide TB initiative

4 September 2011: In a landmark initiative aimed at curbing the current TB epidemic, WHO and FIP signed a joint statement on the role of pharmacists in TB care and control.



*The President of India, with an audience of more than two thousand FIP participants, receives a souvenir brochure of the congress from E.S.L. Narasimhan, Governor of the State of Andhra Pradesh.*



'[This] established a series of measures to help detect TB, offer treatment and support to TB patients, and substantially reduce the number of deaths from TB...by encouraging FIP's network of two million pharmacists and pharmaceutical scientists around the world to become fully engaged in national TB care and control efforts<sup>2</sup>.

### Active student pharmacists

The International Pharmaceutical Students' Federation (IPSF) and its 300,000 worldwide membership have played a large part in developing a vision for the profession, not least in a decade's promotion of patient counselling and the annual international patient counselling competition. The second edition of IPSF's first-class guide to patient counselling was recently announced<sup>3</sup>. The fruits of that work and much more were presented in an impressive session: 'Mapping a new vision - Translating ideas into practice'.

### First time in India

This was FIP's first congress in India and it was massively supported by Indian pharmacists, scientists, academics, officials and industry. There were delegations of over one hundred from China, Denmark, Nigeria, Portugal and, of course, India.

Held in Hyderabad's HITECH City, internet service was excellent, though we foreigners could not buy a local pay-as-you-go SIM card for security reasons. Security was tight everywhere with vehicles, bags, and persons being searched and scanned at the entrance to every location.

## Extracts from the President's speech

"...a very large part of the world's population, mostly in developing countries, has inadequate or no access to healthcare or essential medicines at affordable cost."

"How to achieve access to healthcare and essential good quality medicines for all, at a reasonable cost, must be an essential part of any discussion on pharmaceutical sciences."

"Aware of the enormity of the task of ensuring the safe and judicious use of medicines, the Government of India initiated a National Pharmacovigilance Programme in July 2010."

"In India the flow of pharmacy professionals per annum is 41,000 from diploma institutions and around 50,000 from degree institutions."

"By 2015 [the Indian pharmaceutical industry] is expected to become a US\$20 billion industry, from its present turnover of US\$12 billion. It is already the third largest in the world, by volume."

"I ... believe that we should draw on the rich resources of our indigenous knowledge of medicine ... India has much to offer the world in terms of alternative medicine."

*Speeches of the President are available at: [www.presidentofindia.nic.in](http://www.presidentofindia.nic.in)*

### Sight-seeing and hospitality

For those who had a little spare time, there were visits to Golconda Fort, the Qutub Tombs, Chowmahalla Palace (the residence of the wealthy Nizams of Hyderabad) and the iconic 420 year-old Charminar in the centre of the old city. As ever, there was too little time for such pleasures.

An army of volunteer pharmacy students helped in the running of the Congress and were charming, friendly and helpful. Along with the multiple professional and scientific riches, the entire experience was one to be enjoyed and relished.

Next Year's centenary meeting will be held in Amsterdam, The Netherlands, followed by Dublin in 2013 and Bangkok in 2014.

1 See page 4, Uppsala Reports 54, July 2011. A report on this recent development at the Pharmacovigilance Forum: <http://pharmacovigilanceforum.com/pharmacovigilance-news-and-events/ipc-receives-access-to-who's-umc-for-adr-data/>

2 Quoted from the Congress press release. Link to the WHO/FIP joint statement: [http://www.fip.org/files/fip/WHO/Signing%20ceremony\\_WHO/FIPJointStatement.pdf](http://www.fip.org/files/fip/WHO/Signing%20ceremony_WHO/FIPJointStatement.pdf) The WHO Stop TB Partnership also has an excellent factsheet '2010-2011 Tuberculosis Global Facts', downloadable via [http://www.who.int/tb/publications/2010/factsheet\\_tb\\_2010\\_rev21feb11.pdf](http://www.who.int/tb/publications/2010/factsheet_tb_2010_rev21feb11.pdf)

3 Download the first edition from: [http://www.ipsf.org/uploads/File/pce\\_booklet.pdf](http://www.ipsf.org/uploads/File/pce_booklet.pdf)

## Resistance at EACPT

Ghazaleh Khodabakhshi



The 10<sup>th</sup> Congress of the European Association for Clinical Pharmacology and Therapeutics (EACPT) was held in Budapest on June 26-29. It hosted 42 sessions, seven symposia and two workshops in three and a half days. Over 700 registered participants from 56 countries had the possibility to listen to four

plenary speakers and 150 oral presentations. UMC was represented in the pharmacovigilance session by a presentation entitled 'Resistance and substandard antibiotics: can we detect signals?'. This was based on the results of a pilot study at the Research department, demonstrating a powerful approach for detection of therapy failures indicative of

antimicrobial resistance (as mentioned in Marie Lindquist's editorial in UR53). \*

The national Nigerian pharmacovigilance centre NAFDAC has recently written on its experience of reported adverse drug reactions related to antibiotic therapies, highlighting the complexity in monitoring antibiotic resistance and the need for both global and national responses in order to combat the problem (Pharmacovigilance – FDIC News. Vol 5, no 2, 2011).

\*Abstract reference: Basic & Clinical Pharmacology & Toxicology, Abstracts of the 10<sup>th</sup> Congress of the European Association for Clinical Pharmacology and Therapeutics, 26-29 June 2011, Budapest, Hungary, Volume 109, Issue Supplement s1, page 26, June 2011.

## Child safety

Kristina Star

The UMC was privileged to be represented at the Congress of the European Society for Developmental, Perinatal and Paediatric Pharmacology (ESDP) in Oslo on June 15-17 2011. The ESDP is the leading international society in paediatric clinical pharmacology and is held every other year. At the pre-congress, I presented an overview of reported adverse drug reactions in children and adolescents based on VigiBase data, and at the main conference I spoke on the role of the Uppsala Monitoring Centre and WHO during the session on 'Pharmacovigilance and Drug Safety'. The majority of the attending professionals were clinical pharmacologists, paediatricians and pharmacists from all over the world whose research focus is clinical needs and challenges that the pharmacological treatment of children entails.

# Regional pharmacovigilance journey in Spain

Mariano Madurga

The Spanish Pharmacovigilance System held its XI Annual Pharmacovigilance Journeys on 29<sup>th</sup> to 30<sup>th</sup> September 2011, in Bilbao in the Basque region. Most of the 300 participants were healthcare professionals, those responsible for pharmacovigilance within pharmaceutical companies, and staff from regional pharmacovigilance centres.



Staff of the Spanish Pharmacovigilance System at the Bilbao conference

Topics on the two-day programme included four round-tables:

- Polypharmacy: Rationality and extent of this practice
- Strategies to minimize the risk associated with polypharmacy
- Safe Use of Medicines, ADR, incidents and medication errors
- Research in Pharmacovigilance.

The closing address 'The Role of Regional Centres of Pharmacovigilance in the new scenario of the European Pharmacovigilance' was given by Prof Jean-Louis Montastruc of the Centre Midi-Pyrénées de Pharmacovigilance, Toulouse, France. This important review set out the challenges facing regional centres with the new European Union legislation on pharmacovigilance.

### Awards

The closing session was also the moment to give the annual awards acknowledging those who had contributed to the different aspects of pharmacovigilance activities, signal

detection and training activities. After two awards, to best oral communication and best poster, the 'Premios AEMPS de Farmacovigilancia, 2011' was awarded to the Pharmacy Service of the Hospital of Galdakao-Usansolo, Bilbao, for its development of pharmacovigilance in this hospital and support for the pharmacovigilance unit of the Basque Country region over 25 years. The second prize went to Dr JA Ortega, paediatrician from the Murcia Region, for his contribution to signal detection in paediatric use of medicines.

In May or June of 2013, Tenerife in the Canary Islands will host the XII Annual Pharmacovigilance Journeys. See you there!

Conference proceedings and more information can be found at this website: [http://www.aemps.gob.es/eventos/Congresos/2011/XI-Jornadas-FV\\_septiembre-2011.htm](http://www.aemps.gob.es/eventos/Congresos/2011/XI-Jornadas-FV_septiembre-2011.htm)

# Hard Rock and a little bit of jazz at ICPE

Tomas Bergvall

As ICPE president Dr Stephen Evans reminded delegates in his opening address, ICPE and ISPE go back to the early 1990s and much has been achieved over that time. Dr Evans also stressed the importance of the peer review process in ICPE and now that the conference is so big (a record-breaking

1,150 attendees from 25 countries in Chicago this year) the need to sustain the quality of the work sent to the meeting is great. Dr Evans also discussed the importance of conflicts of interest statements which he urged members to take seriously.

### Trust and democratization

The keynote address was given by Robert Califf, Director of the Duke Translation Medicine Institute in Durham, North Carolina. He felt that the people around us are losing trust both in industry, prescribers and the regulatory authorities due to recent scandals. He questioned whether the systems we are using generate enough evidence needed to make informed decisions. He stressed the democratization of information and that it is important that people do not think they own information.

The 50<sup>th</sup> anniversary of the thalidomide disaster was commemorated by a talk entitled 'Reflections of a Thalidomide Survivor' by Tsugumichi Sato, with personal experiences from the tragedy. Two key

participants in the story, Frances O. Kelsey and Barbro Westerholm, were honoured with lifetime achievement awards.

The UMC was represented by a team of five delegates with one oral presentation in the Methods for Early Detection session entitled 'Fuzzy text matching' which was well-attended. Hot topics at the conference included High-dimensional propensity scores (HD-PS) and the H1N1 vaccines.

With the annual cycle of elections to its board, Marie Lindquist this year has been elected as an ISPE Director.

The meeting also included a night out at the Hard Rock cafe which had a jazzy atmosphere to it and enabled some of the participants to really get their groove on.

After a mid-year meeting in Miami Beach next April, ISPE will hold their 2012 annual conference in Barcelona.



Reflections from ISPE: Mats Persson and Richard Hill in Millennium Park, Chicago

## Xiaofei Ye at UMC

Xiaofei Ye is a PhD student majoring in health statistics from Second Military Medical University, Shanghai, China. He stayed at the UMC from March to September 2011; before his arrival he had begun research focused on signal detection on adverse drug reactions from both spontaneous reporting system and meta-analysis.

### Scholarship in Sweden

Xiaofei was awarded a scholarship in 2010 from the China Scholarship Council, a non-profit organization providing financial aid to Chinese students to study abroad. Luckily Xiaofei got the opportunity to attend Stockholm University and UMC as a joint training PhD student under the supervision of Niklas Norén, who is also the manager in research department at the UMC. The research project is 'Statistical methods to

eliminate the effect of masking in adverse drug reaction surveillance'. He has been working on this project together with Kristina Juhlin and Niklas Norén. The project progresses well and the preliminary manuscript has been finished.

"I would like to extend my thanks to all the staff at UMC. Everyone here is kind and enthusiastic, which makes me feel at home. When I have trouble, whatever in life or research, they are all glad to help me. My knowledge about pharmacovigilance improved during this process. I also like the working environment at the UMC very much."

After the project, Xiaofei will return to Shanghai, where he will start his work as a lecturer at the department of health statistics, Second Military Medical University.



*Xiaofei Ye*

## A sign of our times

*Anette Sahlin*

Exterior signs advertising the existence of the UMC have been an on-going saga. In order to get a sign on a building in Uppsala there are several bureaucratic obstacles along the way. Both at the old address in Stora Torget and now in Bredgränd the UMC has tried to show its physical existence to the outside world.



After much perseverance, the UMC office finally has its location clear to pedestrians and visitors. Following six months of mailing and waiting, our signs are now finally in place and we have definitely signalled our presence in Uppsala!

You are welcome to pay us a visit if you happen to be in the neighbourhood!

## Welcome to Antonio



The UMC has welcomed a new Head of Pharmacovigilance Services, Antonio Mastroianni. He started in September and we look forward to learning about his role in the next edition of Uppsala Reports. Meanwhile, Antonio will be out and about, including the WHO Programme meeting in Dubrovnik.

## Staff departures

We have said farewell to three staff over the last quarter. Britt Gustavsson-McCurdy is taking well-earned retirement, but we expect she will not be that inactive. Richard Hill has moved to the pharmacovigilance department of a pharma company in Australia; and Henrik Sahl has taken a position as Marketing Manager with a Swedish pharmaceutical manufacturer.

We wish all three of them the best for the future.



# Launch of training videos

Worldwide experts on your desk!

Anna Hegerius

You can now access a range of UMC training videos on the internet.

During the UMC pharmacovigilance course in May 2009, a few presentations were filmed and put on the UMC website. The feedback we received was very positive, and it was decided to take the idea further. As a consequence, most of the presentations from our May 2011 course were filmed.

Since the number of places on the pharmacovigilance course is limited, many applicants are disappointed. Others lack the funding or time necessary to go abroad for two weeks of training. Through this e-Learning initiative, UMC aims to meet those needs and reach a much larger audience to increase the global impact of our training.

The web lectures cannot be a complete substitute for the actual course, since live training offers benefits such as group work, interaction with speakers and social networking. The web lectures are, however, a valuable training resource that could be used

in many different settings worldwide by individuals and groups. A statement explaining the intended use of the material is provided on the website, in addition to guides for learning and teaching. A wide range of topics are presented and pdf handouts are also available.

In order to improve this e-Learning portfolio, we are very interested in your opinion of the website.

Feel free to comment frankly on design, functionality and/or content. Please note that these films of live sessions were not prepared and recorded specifically in a studio for internet publication. They have, therefore, some technical weaknesses (particularly the sound of participants contributing to the session),



UMC training now online

but the primary content is almost always clear and straightforward.

Please take a look at the UMC website, under Pharmacovigilance > Education and Training, and tell us what you think. Contact: Anna Hegerius: [anna.hegerius@who-umc.org](mailto:anna.hegerius@who-umc.org).

## Publications news

### Research publications

Johan Hopstadius

A new commentary in *Pharmacoepidemiology and Drug Safety* entitled 'Safety surveillance of longitudinal databases: methodological considerations' has been published. This is a 4-page commentary to an article from the OMOP (Observational Medical Outcomes Partnership) cup winner Martijn Schuemie of Erasmus University Medical Center, Rotterdam. The OMOP Cup was a competition for students to come up with new methods for analysing longitudinal databases which was performed on simulated data. Schuemie's article describing the winning method, had limited references to previous work within the area. Hence the commentary, comparing his approach with the UMC's, examines the strengths and weaknesses of the different approaches.

Noren GN, Hopstadius J, Bate A, Edwards IR. Safety surveillance of longitudinal databases: methodological considerations. *Pharmacoepidemiol Drug Safety*. 2011 Jul;20(7):714-7.

An article describing the core methods related to screening of spontaneous reports and electronic health records employed by the UMC has now been published online ahead of print in *Statistical Methods in Medical Research*. We describe general usage of shrinkage observed-to-expected ratios of which IC in practice is a special case. The article links usage of observed-to-expected ratios between pair-wise measures (IC, ROR, PRR), three-wise measures (Omega), adjusted measures, and contrast measures (ICdelta) with our graphical approaches in database trends and chronographs.

The article also describes a simplified way of implementing the IC which may help to demystify the IC in some audiences!

Noren GN, Hopstadius J, Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. *Stat Methods Med Res*. Epub 2011 Jun 24, doi:10.1177/0962280211403604

### Pharmacovigilance chapter

In UR54 we briefly mentioned the *World Medicines Situation 2011, 3<sup>rd</sup> Edition*, an online reference published by WHO. Many of the chapters in this (including pharmacovigilance) are now live on the WHO website, including topics such as 'Good governance of pharmaceutical sector' and 'Selection of Essential Medicines':

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

### Being a member reprints

The UMC has updated and reprinted the English and French versions of the short booklet for national centres entitled *Being a Member of the WHO Programme*. Apply to [info@who-umc.org](mailto:info@who-umc.org).



# The WHO DD Information Management Section

*Matilda Ahnfelt*

The WHO Drug Dictionaries (WHO DD) are the most comprehensive and actively-used drug reference work in the world – an indispensable source of medicinal product information for drug development and safety surveillance. In drug safety surveillance the dictionaries are used when analyzing the data for early signals of adverse drug reactions and to identify drug names from all over the world, their therapeutic use and active ingredients.

WHO DD contains unique product codes for identifying drug names and evaluating medicinal product information, including active ingredients and therapeutic uses. Users such as clinical research organizations can code concomitant medication and classifications to set up studies, to better analyze, understand and draw conclusions from the resulting data, and to accelerate their submissions to national regulatory authorities.

National regulatory authorities, which have a clear interest in the fast, safe and correct communication of clinical and drug safety data collected from trials and reports from around the world, are also regular users of WHO DD. In September 2011 the dictionaries contained 239,491 unique names and 1,841,271 different products and trade names.

The WHO DD Information Management Section is divided into two teams and is involved in the development and maintenance of the dictionaries to ensure that daily operational processes are performed utilizing highest quality standards for accurate and up-to-date dictionaries. Both teams code medicinal products received via the collaboration with IMS Health. The coding process includes validating and entering the active ingredients, verifying product names and assigning ATC codes.

The Information Management Section also carry out quality assurance projects, map herbal and chemical substances, coordinate activities with regulatory authorities, and assist the UMC Pharmacovigilance department with issues regarding drug information. The teams also develop the processes and the tools used to code the dictionaries, participate in the development of new products and new quality assurance controls, all of which is carried out in close collaboration with UMC system developers.

*As we have yet to be presented to Uppsala Reports readers, we take this opportunity to briefly introduce ourselves, and what we do.*



*Members of the Drug Dictionary Information Management Section (from left): Anna Baumgarten, Anna Andersson, Matilda Ahnfelt, Jenny Klint, Maria And er, Emma Rofors, Madeleine Krieg, Sanna Pettersson*

**Anna Baumgarten**, MSc Pharm, Team leader, is responsible for developing, planning, coordinating and following up team activities. Until recently Anna held a position as a pharmacy manager, and has a history of being a specialist in pharmaceutical self-care. In her spare time you'll find Anna enjoying building her new cottage in the company of family and friends.

**Maria And er**, MSc Mol Biotech, Team leader, is responsible for planning and coordinating the activities within her team. She is also a project manager and requirements analyst. Maria took her master's degree at Uppsala University, and previously worked as a business consultant at IBM. In her spare time Maria is a serial home renovator.

**Emma Rofors**, MSc Pharm, Coding specialist, is a specialist in the Standardized Drug Groupings, SDGs. She develops new SDGs and validates and adds new drugs to existing SDGs every quarter. Emma's roots are in Link oping, but she has lived in Uppsala since 2002. In her spare time she likes to spend time to decorate and renovate her apartment and to be active with different sports.

**Jenny Klint**, BSc Pharm, Coding specialist, is responsible for coordinating the activities with IMS Health. She also validates and enters new information into the dictionaries as well as quality assurance of the content. Jenny is from Sweden's largest island Gotland, a popular Swedish summer resort. On Gotland she doesn't just have her family – but also her horse.

**Anna Andersson**, MSc Pharm, Coding specialist, is responsible for the coding of

products included in reports sent through VigiFlow. Anna also coordinates the activities to manually map the drugs that are not automatically mapped to a product in the DD when Individual Case Safety Reports are sent to the UMC. She previously worked at a pharmacy's customer service department. Anna has a bus driver's licence, and used to be a soccer goal keeper.

**Sanna Pettersson**, MSc Pharm, Coding specialist, returned to her hometown Uppsala in 2009, after spending almost six years in Gothenburg. Her main focus used to be maintenance of the Herbal Dictionary, but her tasks are shifting more and more towards development activities. Sanna still enjoys herbals so to fulfill her interest she is now responsible for the flowers in our office.

**Matilda Ahnfelt**, MSc Med Biol, Coding specialist, returned to her hometown Uppsala in 2003, after her studies at Link oping University. She joined the UMC after being a part of the Human Protein Atlas project. Matilda works with quality assurance, but also tests the internal tools used to code medicinal products and external products, such as the DD Browser. In her free time she is a fitness class instructor and really enjoys making other people sweat.

**Madeleine Krieg**, MSc Pharm, Coding specialist, started at the UMC as a consultant in early 2010, working with the new Chinese dictionary as well as with entering new products into the WHO DD. Currently she spends her time as project leader for internal development projects. The only girl who currently plays floor-ball with the UMC on Thursdays, she is proud to have to run the Stockholm Marathon!

## Chinese Pharmacists' Association

*Anna Hegerius*

The first afternoon of September saw members of the Chinese Pharmacists' Association (CPA) visiting the UMC. The group consisted of 11 chief pharmacists from different Hospitals in Beijing as well as the Director and Associate Director of CPA. One of the pharmacists was also editor of the Chinese Adverse Drug Reactions Journal. After Marie Lindquist had welcomed the group to UMC, they listened to presentations about the WHO Programme, the UMC signal detection process, and traditional medicines. It was a nice meeting and both parties exchanged useful information. In the end of the day, as a token of appreciation, the group handed over a beautiful box with famous Chinese teas.



*Anna Hegerius with visitors from the Chinese Pharmacists' Association on the front steps to the UMC building*

## ... and Chinese pharmaceutical industry

*Zhurong Liu*

On September 6<sup>th</sup> members of the Chinese Pharmaceutical Industry Association (CPIA) came to visit the UMC. Mr Zhang Mingyu, head of the CPIA delegation and their Deputy Director, gave the UMC a short introduction about CPIA and set out what they were interested in hearing from us. The following issues were on their agenda:

UMC's communications mechanism with local government, especially for policy changes. For example, our views on consultation for draft policies being sent around before decision or publication? The organizational structure of the UMC; operational mechanisms; what we will focus on in coming years, as well as better co-operation between UMC and other bodies.

Marie Lindquist, Richard Hill, Annika Wallström and other UMC colleagues attended the meeting and Marie briefly introduced the UMC visions, history, role and functions. Richard introduced how the UMC works with national centres to report and collect ADRs and how we deal with the large number of ADRs and communicate with centres. Annika described the UMC products, especially the drug dictionaries.

The UMC, through training and other support may have a role in emerging countries to assist in developing knowledge in industry. To cope with international requirements both from advanced regulatory authorities and pharma companies in western countries, they need to learn a lot. There was also a lot of interest from the CPIA delegation in signal detection and analysis.



*Zhang Mingyu, Deputy Director of the CPIA and Marie Lindquist, UMC Director*



*CPIA members at the UMC*

Several members of the delegation from Chinese pharmaceutical companies were particularly interested in current pharmacovigilance-related issues. Although large domestic pharma companies have not had many professionals working in pharmacovigilance, the SFDA (Chinese regulatory authority) has issued new rules making it mandatory that all pharma companies in China should have trained and experienced professionals for pharmacovigilance work.

DATES	TITLE	PLACE	ORGANISER/CONTACT
26-28 October 2011	11 <sup>th</sup> ISoP Annual Meeting (preceded by training courses)	Istanbul, Turkey	International Society of Pharmacovigilance www.isop2011.org
28-30 October 2011	6 <sup>th</sup> Asian Conference on Pharmacoepidemiology	Beijing, China	ISPE www.pharmacoepi.org/meetings/ E-mail: ISPE@paimgmt.com
31 October 2011	Drugs in the Environment – Ecopharmacovigilance for better health	London, UK	Organizers: Giampaolo Velo (Italy) and Giovanni Leonardi (UK) E-mail: gpvelo@sfm.univr.it
November 2011 – May 2012	Certificate in Pharmacoepidemiology and Pharmacovigilance	London, UK and distance learning	London School of Hygiene and Tropical Medicine Tel: +44 (0)20 7299 4648; Fax: +44 (0)20 7299 4656 E-mail: shortcourses@lshtm.ac.uk
8-9 November 2011	Training Course on Introduction to Signal Detection and Data Mining in Pharmacovigilance	Berlin, Germany	DIA Europe Tel.: +41 61 225 51 51 Fax: +41 61 225 51 52 Email: diaeurope@diaeurope.org
9-10 November 2011	Case Narrative Writing for Reporting Adverse Events	Southampton, UK	Drug Safety Research Unit Tel: +44 (0)23 8040 8621 www.dsru.org/ E-mail: jan.phillips@dsru.org
18-20 November 2011	11th Annual Conference of Society of Pharmacovigilance, India	Patna, India	SoPi http://sopi2011patna.com/ sopi2011patna@gmail.com
23-24 November 2011	Pharmacovigilance in Products Subject to Licensing Agreements	London, UK	Drug Safety Research Unit (see above for details)
24-26 November 2011	VIII Encuentro Internacional de Farmacovigilancia	Bogotá, Colombia	Departamento de Farmacia, Universidad Nacional de Colombia Tel.: (57-1) 3165000 ext 14623 Fax: (57-1) 316 5060
30 November – 3 December 2011	EuroDURG/ISPE meeting 'Better public health through pharmacoepidemiology and quality use of medicine'	Antwerp, Belgium	University of Antwerp E-mail: monique.esleviers@ua.ac.be http://www.ua.ac.be/main.aspx?c=.EURODURGMEETING&tn=95530
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
7-8 December 2011	Getting to Grips With The New European Union Pharmacovigilance Legislation	London, UK	Drug Safety Research Unit (see above for details)
13-15 December 2011	Pharmacovigilance – A Basic Training Course for those working on drug safety monitoring in the EU, USA and Japan	London, UK	Management Forum Ltd Tel: +44 (0)1483 730008 www.management-forum.co.uk E-mail: registrations@management-forum.co.uk
9 January – 16 April 2012	Drug Safety Et Surveillance	Bath, UK and distance learning	University of Bath (register by 18 November 2011) E-mail: DSS@bath.ac.uk or Tel: +44 (0)1225 386773 www.bath.ac.uk/pharmacy/postgraduate/drug_safety_surveillance/
23-24 January 2012	Latest Developments in Pharmacovigilance	London, UK	Management Forum Ltd (see above for details)
25-27 January 2012	Medical Aspects of Adverse Drug Reactions	Southampton, UK	Drug Safety Research Unit (see above for details)
13-17 February 2012	International Meyler Course in Pharmacovigilance 2012	Groningen, Netherlands	University of Groningen By invitation; CVs and explanation of why you should be invited to be sent by 15 December to Prof AC van Grootheest (ac.vangrootheest@lareb.nl)
13-17 February 2012	DIA Excellence in Pharmacovigilance: Clinical Trials and Post-Marketing Training Course	London, UK	DIA Europe (see above for details)
22-23 February 2012	Monitoring Safety in Clinical Trials and Drug Development	London, UK	Drug Safety Research Unit (see above for details)





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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About UMC > UMC staff – on our website.

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

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