

MUR58



Training in Uppsala | Monitoring innovations

Indian puzzle | UMC visits



When I was a young girl, I read all the Sherlock Holmes stories. I was fascinated by his observational skill - his attention to every detail and its meaning and implication – and how simple the solution seemed once the facts were put together in a logical way.

Maybe my childhood interest had a greater influence on my choice of profession that I first thought. One of the questions in pharmacovigilance – “did the drug do it” – is in essence the same as that which the great detective so often pondered, albeit with a suspect, mostly, being a person, instead of a medicine.

The investigations which had to be undertaken before a verdict of ‘guilty’ could be reached included careful examination of all facts; assessment of temporal relationship, plausibility, and the absence of other explanations. Sherlock said to his loyal friend Dr Watson “when you have eliminated the impossible, whatever remains, however improbable, must be the truth”.

I’m still seeking the truth!

But is there a truth? Isn’t there a risk that we, in search of ‘the truth’, lose ourselves in a futile academic quest, seeking certainty where there is none, and forgetting about the real reason why we do our job – protecting patients from harm.

Bertrand Russell wrote “the law of causality, I believe, like much that passes muster among philosophers, is a relic of a bygone age, surviving, like the monarchy, only because it is erroneously supposed to do no harm”. He was challenging the deterministic view of causality which postulates that “whenever the cause A occurs, then the effect B follows”.

In real life it is very rare to have a situation where there are no alternative possible causes, or where every instance of A causes B.

In these cases we can only establish a probability that A caused B, with a degree of uncertainty around the probability estimate. The probabilistic causation says that A causes B if A’s occurrence increases the probability of B - we can say that a medicine causes rash, although not all rash is caused by medicines. We also need to know about X & Y and their interaction. Does A lead to B only if X is present?

Having abandoned the simplistic deterministic causality, we have to face complex assessments of intricate functional relationships, often with key information missing.

Those who think that such evaluations can be translated into an infallible algorithm, not requiring the critical faculties of an inquiring mind, will always be disappointed and frustrated. We are now grasping at understanding situations sufficiently and with enough certainty to feel confident about important decisions, sometimes even the need to remove a drug from the market.

Falsely attributing a harmful effect to a medicine, or a treatment, will cause a lot of damage, which can be difficult to reverse. For example, the higher prevalence of measles in the UK comes as no surprise given the impact of Wakefield’s claims that there was a possible causal link between MMR vaccination and autism – and are we surprised that parents rejected the vaccine?

The complications associated with measles were not a topic of much interest, particularly not at a time when the successful vaccination schemes had more or less eradicated the disease. The risk of autism, on the other hand, is seen as a real, and horrible, threat by parents, sensitised by frequent media attention to actual, and perceived, childhood disorders.

Although the principles of causality assessment may be relatively straightforward, the application of those principles to an individual case is a philosophical as well as a scientific challenge.

However, even if we cannot unearth the truth, nor evidence ‘beyond reasonable doubt’, to prove a causal relationship in the individual case, finding out as much as possible about WHY a particular patient did not do well on a particular treatment adds to our knowledge, and may help us protect future patients from unnecessary suffering.

The Uppsala Monitoring Centre Research Conference 2012, which you can read about on page 11, discussed and debated not only the fallacies and prospects of causality assessment as it is practised today, but also the big issues - are we doing the right things, and if not, how can we do better? As you can imagine, there were more questions than answers, but also some new insights, and I know an honest and lively exchange of different viewpoints will continue.

These words were my introduction to the Uppsala conference.

A handwritten signature in black ink, which appears to read "Maria Linder". The signature is fluid and cursive.



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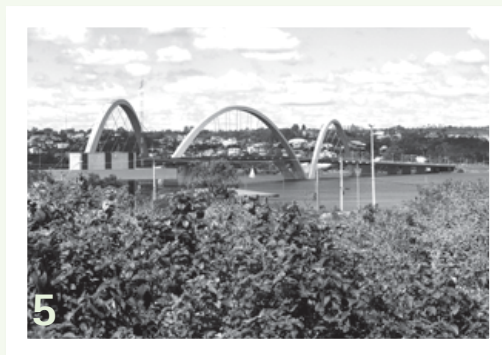
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Reports from national centres around the world



UMC centre of education

Courses and a research conference in Uppsala this May and June

Stimulating the students

How pharmacy students are being introduced to the idea of safety



Eritrea joins the WHO Programme

Mulugeta Russom

Background

Eritrea, a young country located in the Horn of Africa, gained its independence on 24 May 1991 after 30 years of bloody war with Ethiopia. The estimated population of around 3.6 million live in six zones.

The need for a fully functional pharmacovigilance system was set down as early as 1997 in the Eritrean Medicine Policy. In 2001, an officer from the Department of Regulatory Services participated in the biennial two-week training programme on pharmacovigilance organized by the UMC in Uppsala, Sweden. Following the course, gradual steps have been taken to establish the Eritrean pharmacovigilance system:

- A consultancy by Dr Alex Dodoo from Ghana including a four-day National Pharmacovigilance Establishment Workshop, attended by 55 health professionals from all over Eritrea
- Further sensitization programmes (training) in detecting and reporting ADRs
- The Ministry of Health of Eritrea also applied for membership of WHO Programme for International Drug Monitoring in November 2003, thus becoming an associate member
- Some ADR reports were collected from health professionals nation-wide.

In order to foster medicine safety monitoring and rational use of medicines, the Ministry of Health proposed in 1999 to establish Medicine and Therapeutics Committees (MTCs) at national level and in hospitals around the country. The importance of Medicine and Therapeutics Committee is also clearly laid out in the 1997 Eritrean National Medicine Policy. As a result, a few referral hospitals were able to establish and operate the MTCs. The National Medicine and Therapeutics Committee (NMTC) was the advisory committee of the Pharmacovigilance Centre and hence the centre began to make progress. However, because of lack of strong support and follow-up of responsible bodies, the committee ceased its functions. Moreover, when the skilled person in the centre moved to another workplace, there was no one to report the ADRs via VigiFlow.

The Eritrean Pharmacovigilance Programme is coordinated by the Eritrean National

Pharmacovigilance Centre (ENPC), located at the Pharmaceutical Information Unit, Medicines Control Division, Department of Regulatory Services, Ministry of Health, Asmara-Eritrea.



Mulugeta Russom, Head, Pharmaceutical Information Unit, Asmara-Eritrea.

Where are we now?

To tackle the above problems, the Ministry of Health sent two pharmacists, Mulugeta Russom (Head, ENPC) and Iyassu Bahta (Director, Medicine Control Division) to participate in three weeks of pharmacovigilance training and a study tour at the University of Ghana Medical School and UMC-Africa from 26th March to 13th April 2012 (see page 9). Following that training, the ENPC started to function fully and reported 40 ADRs via VigiFlow to the Uppsala Monitoring Centre.

After a few weeks of evaluations, on 23rd of April 2012, the WHO Collaborating Centre for International Drug Monitoring confirmed that Eritrea had become the 107th full member of the WHO Programme. Now the national centre is actively working in sensitizing health professionals to detect and report ADRs. At the same time, the Ministry of Health (MoH) is revitalizing the need for the establishment and operation of a MTC in order to promote medicine safety monitoring and rational use of medicines.

Niger makes 108

The Ministry of Health of Niger applied for membership of the WHO Programme for International Drug Monitoring in April 2011. At the beginning of June this year the national pharmacovigilance centre of Niger submitted its first batch of adverse drug reaction case reports through VigiFlow.

When working relationships are established between the UMC and a national centre the country may be admitted as a full member of the WHO Programme for International Drug Monitoring. Niger became the 108th full member country of the Programme.

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New Associate

In June the Syrian Arab Republic was admitted as an Associate member of the WHO Programme.

Danish merger

On 1 March 2012, the Danish Medicines Agency and the Danish National Board of Health merged into:

Danish Health and Medicines Authority
Axel Heides Gade 1
2300 Copenhagen S
Denmark
sst@sst.dk
Tel + 45 72 22 74 00

Staff e-mail addresses and direct lines are unchanged.

Brazil in sight

This year's local hosts, the pharmacovigilance department (GFARM) of the Brazilian medicines agency (ANVISA) are well-advanced with plans for the 35th annual meeting of national centres, in Brasilia. This modern city boasts a unique urban layout and many iconic 20th century buildings. The venue chosen as the annual meeting venue is 'Brasil 21', near the TV tower in the south hotel sector. All suggested hotels will be within walking distance of the venue. Brasil 21 is the most recent conference centre to be built in the Brazilian capital and offers the latest facilities and much comfort.

Agenda discussion

An on-line questionnaire to national centres, requesting their input to possible topics to be discussed at the meeting, closed at the end of June. In the next few weeks national centres will receive a first draft programme, as well as information on suggested hotels and other advice on attending the meeting.

Translation plans

The last national centres meeting in Latin America was in 2007 in Buenos Aires. Then as now, PAHO, the WHO Regional Office for the Americas, is working with the local host in order to provide simultaneous translation for the plenary sessions, and it is hoped that this will be available into Spanish and Portuguese.

Get ready!

The organisers have already received many indications from national centres which hope to send representatives to the 35th annual meeting, and are looking forward to a successful few days of deliberations. Anyone intending to come should start investigating flights and any visa requirements.



From top : Fountains near the TV Tower, Brasil 21 conference centre, the new National Stadium being constructed, the stained glass interior of the cathedral, shopping at a local craft market

EMP Director

Kees de Joncheere has become the new Director of Essential Medicines and Pharmaceuticals Policies (EMP) at WHO (the department in which the WHO Programme for International Drug Monitoring is situated).

Dr de Joncheere was previously responsible for Health Technology and Pharmaceuticals in the WHO Regional Office for Europe. He worked for 10 years with PAHO/WHO in Latin America and has various publications in the field to his name. He holds Master's degrees in pharmacy and business administration from the Universities of Groningen and Amsterdam, in the Netherlands. Recently Kees de Joncheere has taken an active interest in the Monitoring Medicines project and attended its inaugural meeting at the UMC in February 2010.



Kees de Joncheere speaking at a recent conference in Kiev.

Pharmacovigilance and counterfeiting

Sten Olsson

The 3rd International Scientific and Practical Conference on Pharmacovigilance & Counterfeiting of Pharmaceuticals was arranged by the National Center for Drug Expertise, Kazakhstan, together with partner organizations, in the city of Almaty, from 5-6 April 2012. The scientific programme attracted representatives of many Eastern European and Central Asian national pharmacovigilance centres, including those from Belarus, Kyrgyzstan, Russia, Turkey, Ukraine and Uzbekistan. All the national representatives made presentations of different aspects of their pharmacovigilance and/or anti-counterfeiting activities. The WHO Programme was represented by Sten Olsson from the UMC who talked about pharmacovigilance methods supported by the WHO Programme and the importance of reporting medication errors to pharmacovigilance centres. Pharmaceutical companies, both local and multi-national, presented their pharmacovigilance practices and measures taken to assure the integrity of the medicines supply chain.



Visit to the National Center for Drug Expertise, items for medical practice and medical equipment; from left: Shynar Baydullaeva, Richard Nuber (Boehringer-Ingelheim), Sten Olsson, Raissa Kuzdenbayeva, Arnur Nurtayev, Marat Kiyashev

Many speakers complained about the lack of legal backing for interventions against sub-standard and counterfeit medicines while others noted that implementation of existing laws are ineffective. Several technical solutions for verification of the authenticity of medicinal products were presented. The meeting organizers had arranged for excellent simultaneous translation facilities between Russian and English.

Getting closer to Moscow

Nadja Jastrebova and Jerry Labadie

Nadja Jastrebova and Jerry Labadie from UMC's Pharmacovigilance Services Department visited Moscow, Russia from 17-21 April. We visited both centres that are involved in postmarketing surveillance: Roszdravnadzor (the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation) and SCEMP (Scientific Centre for expert Evaluation of Medicinal Products), and lectured as invited speakers at a conference organized by Roszdravnadzor.

Discussions at Roszdravnadzor

We met Roszdravnadzor staff working with pharmacovigilance: Sergey Glagolev (head) and his colleagues. Sergey described the Russian pharmacovigilance legislation. His centre has pharmacovigilance responsibilities as the regulatory authority. Russian colleagues have a keen interest in signal work on a national level so Jerry explained in detail how Lareb does this in the Netherlands. We were shown the current Roszdravnadzor database which contains approximately 30,000 spontaneous reports. Half the reports are submitted by health professionals and half by pharmaceutical companies. The main challenges we discussed were: how to increase spontaneous reporting and how to make better use of UMC analysis tools.

Roszdravnadzor had organized an international conference for manufacturers of generic medicines entitled 'Quality of medicines and medical devices - The modern requirements and approaches', with more than 600 in the audience. This included presentations on UMC activities in general, and on UMC's approach to management of safety data on generics.

Learning about SCEMP

At SCEMP headquarters we had a meeting with the general director, Alexandr Mironov and representatives of several scientific centres belonging to SCEMP (including vaccines). The hosts explained the position and role of their organization: SCEMP is a scientific body with expertise in data analysis, including ICSRs and possible signals. Anton Pereverzev and Boris Romanov invited us to a Ukrainian restaurant where, over a pleasant meal, we discussed in more detail the analyses they do in the Roszdravnadzor database.

Both centres expressed the wish to intensify collaboration with the UMC in different fields



Nadja and Jerry pause between the Moscow centres

of interest. We are grateful for the opportunity to interact with pharmaceutical companies in Russia during the conference and are very pleased to have been able to meet colleagues from both centres and see the advances they are making with pharmacovigilance in Russia. We were impressed with their enthusiasm and motivation. We have identified areas where we can support their efforts in addition to making UMC tools available in the Russian language (where Nadja has played a key role in the translations). The hospitality of our colleagues and the city of Moscow has made a lasting impression on us and we hope that the intensified collaboration will bring us back soon.

West to East in Africa

Antonio Mastroianni, Cecilia Biriell

In May Cecilia Biriell and Antonio Mastroianni attended the 3rd African Regulatory Conference in Accra, Ghana, which was sponsored by the DIA. The conference offered a broad overview of regulatory challenges in Africa with presentations from key stakeholders active on the continent, including representatives from ministries of health, non-government organizations and local and multinational pharmaceutical companies. The goal of the meeting was to exchange views, discuss topics of interest and identify focus areas for ongoing efforts to increase access to new and improved medicines and to improve patient safety. The main themes were the need for harmonization of standards at a regional level, co-operation in regional African organizations for faster and more efficient approval of new medicines,



At the Pharmacy and Poisons Board in Nairobi: Dr Fred Siyoi, Sophie Waihenya, Christabel Khaemba, Antonio Mastroianni, Leah Mwai, Jayesh Pandit, Mary Njeri and George Muthuri.

strategies to combat SSFFC* medical products, and pharmacovigilance.

Discussions

In addition to attending the conference, we visited the UMC-Africa offices for annual planning and had a chance to have detailed discussions with the staff of UMC-A, and better understand the array of challenges that confront pharmacovigilance. The meetings also identified some common themes that laid a foundation for a strategy of how to obtain more involvement from African countries in the WHO Programme and to stay tuned to major African developments.

Antonio also visited the Ghanaian Food and Drugs Board (FDB). Ms Delese 'Mimi' Darko (Head, Drug Evaluation & Registration at the FDB) and her staff gave him a tour of their facilities, discuss their experiences with VigiFlow, efforts to expand pharmacovigilance awareness across Ghana and their upcoming participation in the UMC's pharmacovigilance course in Uppsala. We also discussed VigiLyze and how it will allow Ghana to perform better



At UMC-A: Cyril, Cecilia, Ama, Sharon, Issifu, Malik

searches and basic signal analysis. This was much sought-after in Ghana as they want to demonstrate the value of participating in the WHO Programme through the enhancement of analysis-based policy-making on medicinal products using statistical outputs derived from the WHO ADR database.

Need for technical support

Throughout the stay in Africa it was clear that the need for a better search and simple analysis tool for VigiBase is extremely high. All national centres are putting their pharmacovigilance departments under pressure to prove value, but showing more reports without the ability to provide analysis provides no value except the acknowledgment of a problem. Search and analysis tools and many of the goals of the UMC's revised signal review process will provide countries with the ability to make better regulatory decisions, reinforce the critical role of reporting standards, and save more patients' lives. The capacity to provide graphs and metrics underlining the value of reporting will be a clear example of the UMC providing technical and scientific support to members of the Programme.

Kenyan initiatives

After Ghana, Cecilia returned to Sweden and Antonio crossed the continent to Nairobi, Kenya to meet Jayesh Pandit, Head of Pharmacovigilance, and learn what the Kenyan Pharmacy and Poisons Board is doing to expand the message of pharmacovigilance. Jayesh and the PPB staff presented their 5-day training course (based on UMC/WHO standards and curriculum), the forms for

ADRs and SSFFC* products, various pharmacovigilance publications, sensitization efforts, and a team that evaluates all advertisements to make sure medicines aren't falsely or misleadingly advertised. Antonio provided a general UMC presentation to Assistant Director Dr Fred Siyoi of the Pharmacy and Poisons Board and to the pharmacovigilance department, and stressed the important role that Kenya plays in East Africa and how Kenya can become a global example of good pharmacovigilance.

The visits were enormously instructive and provided valuable insight into how national centres operate and how the UMC and UMC-A can better support them. Both centres were heavily involved in efforts to improve the quality and efficiency of entering reports in VigiFlow. This presented an opportunity to discuss UMC-based solutions for primary healthcare providers and for patient reporting, which aim to provide seamless entry of high quality data into VigiBase. The increase of reporting, coupled with VigiLyze, holds promise for improved patient safety.

* Substandard/Spurious/Falsely-Labelled/Falsified/Counterfeit (SSFFC) medical products

UMC – SFDA collaboration moves up a gear

Zhurong Liu

In July 2011 the collaborative agreement of Research and Application of Adverse Drug Reactions Standardization was signed by UMC and SFDA (see UR54 page 5). Over the past year, considerable progress has been made by both parties. To consolidate and improve our project work, extensive discussions around the five sub-projects included in the collaboration took place from 14 to 18 May 2012. Six UMC staff, led by Annika Wallström, with Helena Sköld, Madeleine Krieg, Tomas Bergvall, Carl Huddenus and Liu Zhurong, visited the National Centre of ADR Monitoring (NCADRM), SFDA in Beijing. Mr He Li, the representative of Department of International Cooperation, SFDA and Director Dr Du of NCADRM, gave warm welcoming speeches.

Priority

The SFDA authorities gave the meeting high priority, and He Li, Director, on behalf of Department of the International Cooperation, SFDA, and Dr Du Xiaoxi, the Director of NCADRM and 12 of her colleagues attended the meeting.

Two-way presentations

In general, most of the sub-projects have reached expected targets and the upcoming milestones are on track. Over the five days, Tomas, Helena and Madeleine held training sessions in signal detection, analysis and VigiBase database-related introductions for SFDA personnel. The staff of China ADRs Centre presented their system of ADR reporting and monitoring in China.

We all agreed that the meeting and the training sessions had enhanced the understanding of both parties' processes which will be useful in the continuing collaboration.



Annika Wallström and Du Xiaoxi exchange gifts at the meeting in Beijing

DIA in Shanghai

From 20–24 May a DIA conference was held in Shanghai, attended by more than 1,000 delegates and 50 exhibitors. Mats Persson, Madeleine and Zhurong attended the conference and the UMC booth attracted the attention of a lot of Chinese and international CROs, along with electronic data capture (EDC) vendors. One of the significant changes in visitors to the UMC and other booths was that more EDC companies were present and professionals from these companies talked to us about the possibility of having the WHO Drug Dictionary Enhanced in their system. EDC systems are mainly used for clinical trials to rapidly collect data in electronic format. EDC systems have almost replaced traditional paper-based data collection methods because they can collect information in a rapid, accurate, and more time-efficient way and this trend is occurring in China. In the data management of ADRs related to clinical trials, basic elements of the system are case report form, drug information, medical terms and ATC, etc, all important features of the WHO Drug Dictionaries.

Further meetings were held with the Centre for Clinical Trials at the Shanghai University of TCM (Traditional Chinese Medicines), with a local CRO and with a new EDC vendor.



ACSoMP committee 2012 – standing: Ralph Edwards, Ambrose Isah, Jürgen Beckmann, Y.K Gupta, Gerald Dal Pan, Sten Olsson, Claudia Vaca Gonzalez, Alex Doodoo, Pia Caduff-Janosa, Yan Min, Gunilla Sjölin-Forsberg, Ken Hartigan-Go; sitting: June Raine, Shanthi Pal, Marie Lindquist

9th WHO Advisory Committee

Sten Olsson

This year's WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) meeting was held in Geneva from 3–4 May. It was opened by Gilles Forte, Acting Director of the Essential Medicines and Pharmaceutical Policies Department, WHO and was chaired by Gerald Dal Pan, FDA, USA.

The agenda of the 9th annual meeting included the following:

- Reports from WHO headquarters and WHO Collaborating Centres
- Experiences with the Pharmacovigilance Toolkit
- Procedures for reviewing safety concerns by ACSoMP
- Harmonizing pharmacovigilance data submissions
- Proposed processes for submission of ICSRs from EudraVigilance
- Detecting, analyzing and preventing medication errors within pharmacovigilance centres
- Pharmacovigilance of medicines recommended for use by WHO
- Pharmacovigilance of anti-tuberculosis medicines
- New tools for reporting by the public/consumers
- Toxicity monitoring in routine anti-retroviral therapy (ART) programme implementation

- Safety of anti-malarials; proposed updates to the summary of product characteristics of artesunate/amodiaquine combination products
- Piloting pharmacovigilance indicators in selected countries
- Update on the Global Vaccine Safety Initiative
- Collaborations to combat Substandard/Spurious/Falsely-labeled/Falsified/Counterfeit medical products (SSFFC)
- Reporting of drug ineffectiveness.

A more detailed account of the ACSoMP deliberations will be provided in a future *WHO Pharmaceuticals Newsletter*.

Kenya hosts Africa pharmacovigilance meeting

Jayesh Pandit¹, George Muthuri¹, Edward Abwao¹, Janet Kimeu² and Ndinda Kusu²

Kenya was once again privileged to host an important global conference on enhancing patient safety. The conference, dubbed the Africa Pharmacovigilance Meeting 2012 – Ensuring Quality and Safety of Medicines in Sub-Saharan Africa, was hosted by the Ministries of Health, Kenya; the Pharmacy and Poisons Board (the National Medicines Regulatory Authority in Kenya); the USAID-funded, Management Sciences for Health (MSH)-led, Systems for Improved Access to Pharmaceuticals and Services (SIAPS) and Health Commodities and Services Management (HCSM) programmes.

The meeting, on 18-20 April 2012, brought together partners from the African Medical Regulatory Authorities, World Health Organization, Bill & Melinda Gates Foundation (BMGF), European Medicines Agency (EMA), Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), U.S. Agency for International Development (USAID), and other key stakeholders.

During the conference, a recent publication entitled: *Safety of Medicines in Sub-Saharan Africa: Assessment of Pharmacovigilance Systems and their Performance*, was launched and disseminated. The publication addresses the pharmacovigilance systems gap and provides a comprehensive description and analysis of these particular systems and their performance in sub-Saharan Africa.

Country representatives were provided with a platform to share their current practices on pharmacovigilance and thereafter held intense discussions on common needs and opportunities for systems strengthening, collaboration amongst stakeholders in monitoring the quality and safety of products in the supply chain and identification of frameworks and operational tools for the same.

The National Pharmacovigilance Centre in Kenya exhibited various books, reports, resource materials and subscription materials in collaboration with the WHO, Uppsala Monitoring Centre and International Society of Pharmacovigilance (ISoP).



Delegates through Kenya's National Pharmacovigilance Centre stand where locally developed training material, job aids and IEC materials were exhibited and distributed alongside resource material from WHO, UMC and ISoP.

1. Pharmacy and Poisons Board
2. Management Sciences for Health/Health Commodities and Services Management Program

Eritreans study tour with UMC-A

Sharon Ako-Adounvo

As part of the efforts to build pharmacovigilance capacity in Africa, the UMC-A offered three weeks of training to Mulugeta Russom and Iyassu Bhata of the Eritrean national pharmacovigilance centre. The training held in Accra at the UMC-A conference centre was organized and facilitated by expert technical staff of the UMC-A. Interactive teaching covered building an effective pharmacovigilance system, case causality assessments and signal detection, risk and crisis communication. In-depth training was also conducted on the use of data management tools, VigiFlow and CemFlow. There was a rich discussion on the design of ADR forms to stimulate ADR reporting in Eritrea. Participants were tasked to develop initiatives that will increase the number of reports received at the centre. The current Eritrean national centre ADR form was evaluated and suggestions for improvements made; incorporating mandatory data entry fields in order to improve report quality and validity.

The three-week programme included a visit to the Ghanaian National Centre and the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance situated at the University of Ghana Medical School.

See also page 4.

Updating at ANVISA

Elki Sollenbring

The pharmacovigilance team at the Brazilian national medicines agency invited the UMC to provide training in tools and methods at their headquarters building in Brasilia. I spent three days in June taking key staff from GFARM (the pharmacovigilance unit) through VigiBase, VigiSearch and other related issues raised by Giselle Calado, head of the unit, and her team. I learnt about some of the challenges they are addressing in their daily work for this large and fast-developing country.

There was also a video conference about the WHO Programme for International Drug Monitoring for the national network of hospitals (188 hospitals - Sentinela em Açã). Members of the GFARM team were very hospitable during my short stay.

Access to global ICSR data

Antonio Mastroianni

The UMC and WHO are formulating a comprehensive data access policy for the WHO Global Individual Case Safety Reports (ICSR) database, VigiBase.

The recommendations from the Advisory Committee for Safety of Medicinal Products (ACSoMP), which were established in April 2011 and re-affirmed in May 2012, underline that the process of opening access would need to be done in a responsible, stepwise fashion. Some extensions will be made to the current data retrieval interface being used by national centres, by a new search tool. The aim is that those who are not members of the national centres will be able to log on to VigiBase, but with a different level of access, for example, to some summary tables. The UMC is preparing to make these summaries available. The full ACSoMP statement is available on page 2 of their report via WHO's website: http://www.who.int/medicines/areas/quality_safety/safety_efficacy/recommendations.pdf

At present, signals are published in the UMC Signal Document and through the WHO publication, *WHO Pharmaceuticals Newsletter*. VigiBase summary data will meanwhile be made accessible via the UMC web page (www.who-umc.org) in the near future.

Presently, all data from case reports in VigiBase are available to anyone with a health professional degree-level education (physician, dentist, nurse, pharmacist) and can be ordered by request. All recipients of data from VigiBase must accept the conditions for use stated in the UMC Caveat document. Searches in VigiBase are performed by the UMC on request, free-of-charge for staff at national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring, which also have access to all reports in VigiBase via an online search tool. The 'Caveat document' still remains a key feature in the use of VigiBase.

The intention of WHO is that the more than 7 million reports in VigiBase, from national pharmacovigilance centres around the world, be made accessible in a responsible, stepwise fashion in order to assist early detection of problems with medicines. Publishing the UMC signal document (SIGNAL) in *WHO Pharmaceuticals Newsletter* (since March 2012) is the first step toward this goal.

Web-based prescription and adverse event monitoring

Demet Aydinkarahaliloğlu

In order to continue increasing the knowledge about the important identified and potential risks of medicines it is essential to take additional on-going measures. Web-Based Prescription and Adverse Effect Monitoring System is one of the notable models of these measures. This system is a drug risk management method developed by the Turkish Pharmacovigilance Center (TUFAM) and currently being used successfully in Turkey. The main aims of the system are to monitor the prescriptions made after establishing the drug benefit/risk assessment by physicians, and provide continuous monitoring of adverse effects.

In the system, determination of the risk factors is based on the last approved summary of product characteristics of the drug and patient characteristics. Physicians fill in a web-based form that asks them to enter their patients' details and then to check the listed contraindications one by one to determine whether the patient has any of them. If the physician marks a situation that is contraindicative to the use of the drug, a pop-up message warns the physician not to prescribe the drug. A similar section for 'special warnings and precautions for use' is also included in the system. As a final step, the physician declares that he/she had been informed about the safety warnings and contraindications related to the drug, will or will not prescribe the drug, has written the prescription accordingly (if he/she is going to prescribe it), and has informed the patient about its adverse effects.



Demet Aydinkarahaliloğlu

The adverse effects are recorded in the system when reported to the physician by the patient who has been prescribed the drug. Since the system directs the physician through consecutive questions and warns about missing information in the adverse effect form, it offers the opportunity to increase the quality of information and the completeness of the ADR reports. Forms more specific to the adverse effects that have the highest incidence with the prescribed drug are also available in the system. Every adverse effect entered into the

system by a physician is submitted automatically to the e-mail addresses of TUFAM and the marketing authorization holder at the same time. Thus the system facilitates prompt and continuous monitoring of adverse effects.

Setting up a web-based prescription and adverse effect monitoring system was made mandatory by the Turkish Medicines and Medical Devices Agency for the licensing of new drugs with important identified or potential risks where there was a lack of drug safety information. Currently a study is being conducted on making use of the web-based system for prescription of these drugs a prerequisite for reimbursement, in order to achieve involvement of physicians.

There are four medicines for which this system was applied during licensing or post-licensing period: rivaroxaban, eltrombopag, dabigatran and fingolimod. The system will shortly be applied to two new medicines that are currently undergoing licensing procedures. The system works successfully in collaboration with Turkish physicians. At TUFAM, we give much importance to expeditious examination of risk factors and making decisions through an established system before prescribing drugs, to guarantee safe use of drugs, and we are planning to extend the use of this risk management method.

Intensive monitoring doctor

Eugène van Puijenbroek

Linda Härmark, an employee at the Netherlands Pharmacovigilance Centre Lareb, defended her PhD thesis entitled 'Web-based intensive monitoring, a patient based pharmacovigilance tool' on June 4 at the University of Groningen, the Netherlands. Her supervisors were Kees van Grootheest, Professor of Pharmacovigilance, and Han de Gier, Professor of Pharmaceutical Care.

In her thesis, a method (Lareb Intensive Monitoring, LIM) which follows first-time users of certain drugs over time by means of a web-based questionnaires, is described and validated. The studies in this thesis

demonstrate that the LIM system is not only feasible but that it works well in daily practice. With LIM it is possible to collect more detailed information about the user of the drug (demographic data and indication for use), drug use (dosage, use and co-medication) as well as adverse drug reactions (new ADRs, time course of ADRs). Web-based intensive monitoring is a valuable addition to the current methods used in pharmacovigilance.

If you would like a copy of the thesis please mail your address to: info@lareb.nl



Dr Linda Härmark

Causality from all angles

Kristina Juhlin

On the 24th and 25th of May, the Uppsala Monitoring Centre gathered an impressive line-up of international speakers to examine the complex issues surrounding causality assessment during its two-day research meeting 'Causality assessment in an evolving pharmacovigilance landscape'.

Day one focused on the principles of causality assessment within core pharmacovigilance activities; while the second day concentrated on the implementation and effects of causality assessment from the perspectives of those who work with realizing the causality assessment process into actual decisions, and those affected by these decisions.

UMC's director Marie Lindquist opened the meeting with an inspirational welcome address (see page 2), after which Samir Okasha, a professor of the philosophy of science, gave a thorough overview of the philosophical and historical background to the concept of causality in science. From this the meeting went on to discuss the realization of causality assessment within pharmacovigilance and pharmacoepidemiology. The day concluded with a presentation on the accommodation of causality considerations in benefit-risk assessment by UMC's Ola Caster.

The second block of the conference started with an enthusing talk by Mary Baker on

how signals are perceived by the patient community, before looking at the challenges of implementing real-life causality assessment as a regulator, within the pharmaceutical industry, as the legal representative of patients, and when working within a drug relief system.

The final speaker for the day, investigative journalist Mads Ellesøe, presented an open-hearted overview of the decisions involved in publishing a finding on a possible adverse effect, giving the subsequent debate a flying start in the process. The debate, chaired by Ralph Edwards and Niklas Norén of the UMC, concluded the meeting and summed up the variety of pharmacovigilance perspectives represented at the meeting.



Robin Ferner

...an attentive audience

Miriam Sturkenboom

Samir Okasha in conversation with Ralph Edwards

After thoughts

Daniel von Sydow

In medicine it is nearly impossible to say that a drug has caused a reaction – the result of an assessment is more often a 'probability of causality'. Causality assessments are important. All knowledge is based on a reasonably likely relationship between cause and effect. This knowledge is necessary when decisions are made.

One such situation is when a pharmaceutical company and a regulator negotiate a withdrawal or label change. It is important for both parties that the causality assessment is correct – and that the right definition of risk population is made. Another is when a doctor and a patient decide on a treatment. In these situations it is important that the knowledge and decisions are well communicated from the experts in the pharma industry and regulators to healthcare professionals and the general public.

My impression from the conference debate is that causality means very different things for the different stakeholders. The pharma industry and regulators use single case causality assessments to identify events that are useful input when the knowledge about a drug grows – to try to predict future problems.

Litigation lawyers investigate what a pharma company and a regulator could have known 'at the time'. In hindsight it may be clear that certain patients had been put to an unnecessary risk – but was it possible to know that when the drug was approved on the market and when a doctor prescribed a drug? Media also has a 'hindsight perspective' – they find individual cases and make a story. Media can give the public useful information – to be used in situations when doctors and patients decide on a treatment,

but often base their stories on sensationalism, blame-game and victimization.

It would be interesting to see this discussion developed: when are companies or regulators liable and when is it legally acceptable to be unaware of a problem? Is it acceptable to hesitate to communicate a problem before a signal is investigated? Would lawyers and media work differently if they knew more about how the causality assessments are made and the uncertainties in any risk estimation?

On course for sun and showers

Johanna Stenlund

After much anticipation, May finally arrived and so did the participants of the 14th pharmacovigilance course hosted by the UMC in Uppsala, Sweden. A difficult selection process led to 35 participants from 29 different countries being welcomed on the course. They were mainly from national pharmacovigilance centres and other departments within ministries of health, but also Clinical Research Organisations, hospitals, universities, pharmaceutical industry and the WHO Regional Office for the Eastern Mediterranean.

The group possessed an excellent mix of pharmacovigilance experience, which they more than willingly shared with each other. Interactive sessions were something that the course management had strived towards and these turned out to be a great success with this group. Uppsala offered a sunny first week so that people started asking why we had recommended them to bring coats and knitted hats. They didn't know what was yet to come...

Website and pre-course test

Prior to the participants' arrival, a new website was launched that contained basically everything related to the course, which this year included mandatory pre-reading material and some video recorded sessions from last year's pharmacovigilance course that the participants needed to watch prior to arrival. This enabled more interactive sessions in the agenda, where the participants

could discuss the videos with a facilitator. For the first time a pre-course test relating to the reading material was created, that the participants needed to pass. The website was highly appreciated as it enabled the participants to find very useful pharmacovigilance material and prepare themselves well for the course, and also made possible easy communication between participants and course management.

First week

The Module 1 agenda contained several discussion sessions, starting with "The scope of pharmacovigilance and how to look forward"- a highly interactive workshop led by UMC director Marie Lindquist. This set the standard for the rest of the week since the group continued to be very active and discussion-orientated.

The first week contained sessions about the WHO Programme, how to establish a pharmacovigilance centre, different aspects of ADR reporting, pharmacovigilance in public health programmes, regulatory aspects of pharmacovigilance, pharmacovigilance teaching, terminologies, signal detection etc. It might appear like an information overload but the participants still kept asking for more and several evening sessions were arranged.

One day was dedicated to a computer seminar with a discussion regarding data retrieval and what kind of statistics you wish to gain from your database. Various data management systems were discussed and it was very interesting to hear how these differ from one country to another. A lecture was given on VigiFlow and the participants had a hands-on session regarding data entry.

During the causality day the participants were guided through the basics of causality assessment by two of the doctors at the UMC: Jeremy Labadie and Ralph Edwards. Since an important part of the work, both at the national centres and other pharmacovigilance workplaces, is related to causality assessment and how to go from signal to regulatory action, this was a heavy but important day for the participants.

Spare time? Not so much...

The course had a rather heavy schedule this year and with the additional requested sessions, the participants ended up having very little spare time. A few UMC 'Open Houses' were arranged in the evening, where the participants and UMC staff had a great opportunity to mingle and exchange contacts and experiences.

Socializing? A lot!

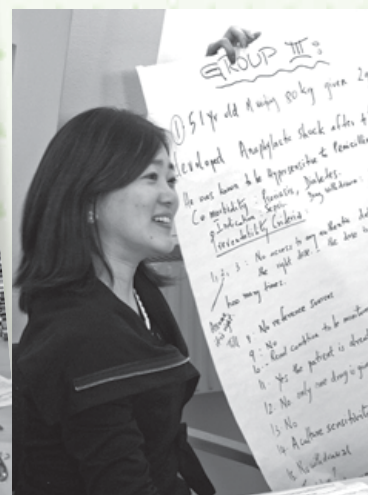
The course dinner was arranged on the birthday of Linnaeus this year, so what could be better than celebrating with him? It was a lovely



Ice-cream stop at Fjällgatan with a view over Stockholm



Workshop about the P method



Workshop results with Sof

summer evening and all the course participants gathered by the Orangery in the Linnaeus garden together with parts of the UMC staff and lecturers. The entertainment consisted of a harpist and Linnaeus himself, along with delicious food and great company.

A trip out

On Sunday most of the participants took a bus to Stockholm, in fantastic Swedish summer weather. A guided tour of the City Hall was followed by an ice cream stop at Fjällgatan with fabulous views over the capital and the water, and a walking tour in the Old Town. A lovely day ended with dinner at Antonio Mastroianni's (head of the pharmacovigilance department) house in the countryside outside Uppsala. For many of the participants this was their first visit to a Swedish home and it turned out to be highly appreciated.

Chilly second week

The following week the participants suddenly realized why packing warm clothes had been recommended. Weather in Sweden can be really unpredictable during this season, sometimes it is 25°C and sunny, then it can drop down to 5°C and rain. (So, if you plan on visiting us in May next year, be prepared!)

This year we had the pleasure of hosting several external lecturers who were new to the course. Andrew Herxheimer spent a few days with the course

and gave a very interesting and interactive lecture regarding patient reporting from the patient's perspective.

For the first time we welcomed Rachida Soulaymani, head of the newly-created WHO Collaborating Centre in Morocco. She discussed medication errors and taught the P method (preventability method) which was developed by the Moroccan team. Rachida's centre hosts an annual pharmacovigilance course similar to the UMC course but for Francophone countries, to be held this year in September in Rabat, Morocco.

Sharon Ako-Adounvo from UMC-Africa was not only a course participant but she also gave an interesting lecture regarding drug counterfeiting and patient safety problems, followed by a discussion session.

A few of the participants left the course after finishing module 1 but most stayed on for the second module and were joined by new participants.

Second modules take off

During the second week new faces arrived to participate in either:

Module 2a: Pharmacoepidemiology, hosted by Professor Toine Egberts from the Netherlands, or

Module 2b: Effective communications in pharmacovigilance, facilitated by UMC consultant Bruce Hugman.

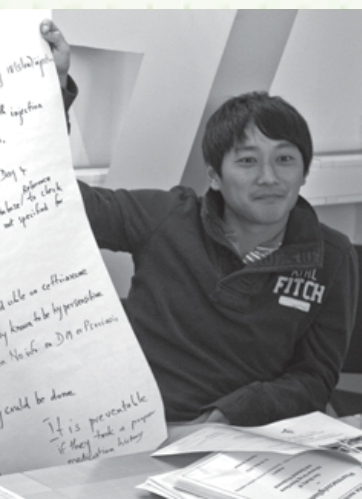
Both modules contained lectures, workshops and discussion sessions. Along with other tasks the participants in 2a created their own pharmacoepidemiology studies, while those in 2b created plans for a communications project within pharmacovigilance.

Thanks from the UMC

Everyone arrived to Uppsala with high expectations on the course and it seems that the participants left filled with new ideas and eager to battle the elements of pharmacovigilance back in their own countries.

On behalf of the course management I would like to thank all the participants for two fantastic weeks. You all shared your experiences, discussed with great passion and contributed to making this course quite extraordinary. Thank you all for making the two weeks even better than we expected!

For those of you who missed the opportunity this year, keep an eye on our UMC website for the course announcement in a few months and prepare your applications well in advance. Hopefully we will get to meet you in May next year!



Hyeon Ahn and Sangook Kim



Pharmacovigilance course managers Anna Hegerius and Johanna Stenlund



Open discussion with lecturers

US FDA Vaccine Safety Seminar

Jerry Labadie

The U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER), Office of Biostatistics & Epidemiology (OBE) ran a two-day training seminar on 2 – 3 June in Uppsala, Sweden. This seminar, 'Application of Pharmacovigilance to U.S. FDA Regulatory Decisions for Vaccines' was open to participants attending UMC's Pharmacovigilance course. Most participants who attended the two weeks of the UMC course welcomed this unique first time opportunity and stayed on for the weekend FDA seminar. This meant two more intense days after a full and demanding pharmacovigilance course but the participants were well rewarded for their stamina and dedication. During the animated discussions they didn't show any signs of 'course exhaustion'. On the contrary, their active participation stimulated the four FDA

- understand the strengths and limitations of data sources used by FDA scientists to assess vaccine safety
- understand the US regulatory authorities relevant to post-marketing surveillance
- recount the role that data sources and regulatory options played in several recent FDA decisions regarding vaccine safety
- find publicly available FDA vaccine safety assessments posted on the world wide web and understand the context for FDA's public communications regarding vaccine safety.

The participants were taken on a tour through the landscape of FDA regulatory safety activities for vaccines. Starting with pre-

vaccines and biologicals were described. The strengths, limitations and use of VAERS (Vaccine Adverse Event Reporting System) the database of the US national vaccine passive safety surveillance program were discussed extensively. The data mining tool (called Empirica) to detect potential signals, and different methods to conduct periodic safety reviews and product based monitoring and evaluation of the data in VAERS, were explained and discussed, with examples. An extensive overview was presented of the range of FDA's active surveillance programs and epidemiological studies in which databases with healthcare information of millions of US individuals are used to actively look for or refine potential vaccine safety signals. All illustrated and clarified with real life examples of FDA's recent experiences



Participants and lecturers at the FDA Vaccine Safety Seminar

facilitators, David Martin, Jerald Mullersman, Scott Winiacki and Craig Zinderman, all physicians. When one of them presented a topic the others joined the discussion which made the interaction with the participants very lively.

Objectives

The course set out to introduce the methods that FDA CBER scientists use to assess post-marketing safety data for vaccines and to communicate subsequent regulatory actions taken. Learning objectives for the course were to:

- understand the structure of FDA CBER and its efforts to improve vaccine safety

licensure safety assessment during the consecutive stages of vaccine development and ending with sources and key decisions in safety and pharmacovigilance planning throughout the life cycle of a vaccine. Required post-marketing studies are a relatively new tool in FDA's safety assessment: the options and considerations for implementation were illustrated by detailed examples and it was shown how the study design should be tailored to answer the safety question and the needed degree of certainty.

VAERS

The FDA's strategies to use passive and active post-marketing safety surveillance of

with safety issues of vaccines and biologicals. The 2-day course provided a comprehensive overview of FDA's activities in the area of safety surveillance of vaccines and biologicals. It will help the participants to understand more of the background of communications and publications the FDA produces regarding the safety of these products. The overview and explanation of publicly available FDA resources on the internet will prove to be a great help to the participants in their own pharmacovigilance activities. One of them I would like to share with those of you who were not able to participate: VAERS data can be freely accessed at <http://wonder.cdc.gov/vaers.html>.

Raising awareness or changing behaviour?

The story of increasing Croatian ADR reporting rates

Adriana Andrić, Darko Krnić, Viola Macolić Šarinić,

The story of continuous growth in the number of adverse drug reactions reports in Croatia began in year 2005, when the National Pharmacovigilance Centre, which was previously part of the University Hospital in Croatia's capital Zagreb, came within the Croatian Agency for Medicinal Products and Medicinal Devices (HALMED). With one major requirement being fulfilled – adequate staffing – the Centre was able then to commit to the nourishment and further development of the ADR reporting culture in the country.

Quantity with quality

With a population of about 4.5 million, the reporting rates in 2005 and 2006 were approximately 150 per million inhabitants (Figure 1). The quantity of reports was already satisfactory, as well as their quality. According to the UMC's documentation grading system, the average completeness score over the period 2007 - 2011 for ICSRs in VigiBase is around 0.75 for Croatia, against an average score of around 0.5 for all countries. The majority of ADRs in Croatia are reported to the National Centre directly by healthcare professionals, up to a quarter of reports come from marketing authorization holders, and an as yet modest number of reports come from patients.

Back in 2005, while keeping in mind the importance of maintaining the quality of reports, our pharmacovigilance team put their efforts into increasing the quantity received. Our target population was

healthcare professionals – primarily physicians and pharmacists. Very soon we learned major lessons of social marketing, with the difference between raising awareness and making the behavioural change of our target population being the most important lesson learned.

Inform and motivate

What do we mean by this? Besides being informed, which is the prerequisite, healthcare professionals need also to be motivated to report ADRs. The concept of raising awareness, as appealing as it sounds in many public health or social programmes, far too often represents just sending the information out there, without clarification on what should one do with it and, most importantly, why.

So, soon after informing the healthcare professionals about the change in the National Centre, we decided to take a proactive approach. The major features of this were direct communication, clear messages, continuous contact, appropriate incentives and reporting back to the reporters. The major activities we undertook, which became our everyday practice, included series of workshops on ADR reporting as well as sending written replies to the reporters for every ADR report received. We have learned that the direct communication with clear messages through ADR reporting workshops for healthcare professionals is the best way to transfer not only the information, but also the

motivational impulse. Using real life examples, ranging from the thalidomide disaster back from the 1960s through to current pharmacovigilance issues, is our way to motivate healthcare professionals for ADR reporting because it makes them realize that they really can make the difference.

An integral part of healthcare

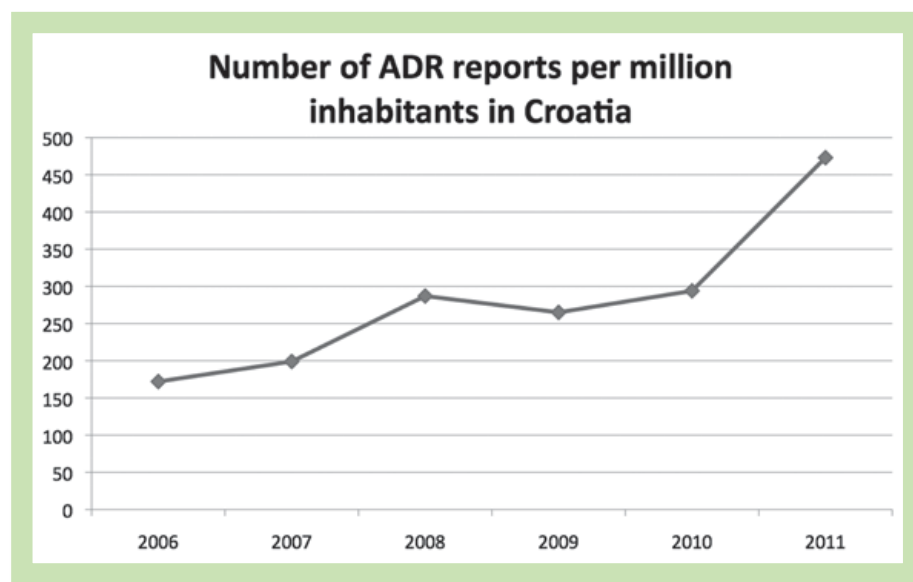
Over recent years, we have held more than 80 workshops with a large total number of participants, reaching approximately 5-10% of all pharmacists and physicians in Croatia. Sometimes it felt somewhat like a pilgrimage, travelling across the country in order to train even the smallest groups of participants, but this continuous contact with healthcare professionals was worth the effort. Written replies to the reporters include the evaluation of the specific ADR and the action that has been, or needs to be taken, as well as relevant data from the literature search. Besides the written feedback, to keep each health professional motivated for further ADR reporting the second major incentive is continuous professional education credits awarded by both the Croatian Medical Chamber and the Croatian Chamber of Pharmacists, which are proof that professional bodies in Croatia recognize ADR reporting as an integral part of providing healthcare services.

Continuing the ascent

Today, while maintaining the quality, we have more than doubled the number of reports. Even though there is still room for more progress in both the quantity and quality of reports, we are now focussing on encouraging direct patient reporting, and have decided to participate in the pilot testing of patient reporting tool with support of the UMC.

Although pharmacovigilance is not generally compared to crossing the Alps (with or without elephants), we would conclude with the quote by Punic commander Hannibal: "Aut viam inveniam aut faciam", which is Latin for "I shall either find a way or make one".

Figure 1. ADR reporting rates in Croatia



ISoP sets the scene for the future

Marie Lindquist and Bruce Hugman

During a fine, summery June weekend in Berlin, following on from two ISoP training courses, the outgoing ISoP Executive Committee (EC), and the three past presidents, held a strategy planning meeting to lay the foundations for the next phase of the Society's development. The resulting proposals will be handed on to the first meeting of the new EC in October for their further consideration and action and ultimately for approval by the ISoP membership.

worldwide; the priority of education and training; the international scope of membership; and the tradition of friendly, productive meetings and networking.

Expansion of the membership and its international reach was seen as a major objective. This was to ensure both genuine representation of international pharmacovigilance interests, and to improve revenue; only on the basis of stronger finances could

such as India, China, Africa and Latin America, was high on the agenda of urgent issues.

In its first decade, ISoP had achieved much, not least survival and expansion across the globe; the organisation of successful meetings and training courses; active contributions to the development of the science of pharmacovigilance. However, there were still many opportunities for improvement, including a wider and more geographically representative membership; more secure funding; a higher profile and greater impact on pharmacovigilance thinking and practice.

An expanding, high-profile future will demand a more pro-active communications strategy for both internal and external audiences. Alternative sources of funding need to be explored, bearing in mind the need to fully protect ISoP's independence and impartiality.

The aims and objectives of the Society were developed and refined in simplified new Vision and Mission statements, presenting the high level essentials for public view.

In all, substantial progress in thinking and planning was achieved, but its ultimate usefulness will be determined by the energy and effectiveness of the next EC and, of course, on the approval and engagement of the members. Serious results should start to become evident after the General Assembly in Cancún in October.



Ulrich Hagemann (standing left), local host, with the course faculty and members of the ISoP Executive Committee relax after their strategic deliberations in Berlin

The group reaffirmed its commitment to the basic aims and values of the Society - primarily the focus on the development of the science and profession of pharmacovigilance

the development ambitions of the Society be pursued. Addressing the challenge of making membership of ISoP attractive and worthwhile across the globe, including major territories

Future collaborators

Johanna Stenlund

In April I had the pleasure of being invited as a guest lecturer at Aalborg University. Aalborg is a Danish industrial and university city, located in North Jutland. The city has a population of slightly more than 100,000, making it the fourth largest city in Denmark. More than 14,000 students are enrolled at the university with 6,500 at the Faculty of Engineering, Science and Medicine. The lectures were given to students who came from the MedIS programme (Medicine with Industrial Specialization) and most of them planned to work within Clinical Research Organizations or pharmaceutical industry, mainly with clinical trials or regulatory affairs.

The lecture consisted of a presentation of the WHO Programme, an overview of the UMC mission and main tasks and the role of our different departments. Only a few of the students had heard previously about the UMC and the WHO Programme while most were hearing about it for the first time. Taking account of the students' career plans, an introduction was also given about the WHO Drug Dictionaries, WHO-ART terminology and VigiBase Services. These tools and services would certainly be of use in their future work places. Who knows, in the future one of them might be our colleague, collaborator or customer?



Getting the message through in Aalborg

Miami sun illuminates ISPE mid-year meeting

Maribel Salas, Abraham Hartzema

"Nosotros, los de entonces, ya no somos los mismos." ("We, of that time, are no longer the same") Pablo Neruda

Some years ago, ISPE (International Society for Pharmacoepidemiology) discussed the role of the Society in the globalization movement, and concerns were raised about the limited human and physical infrastructure in many parts of the world to carry out pharmacoepidemiologic studies. Time has gone by, and we are facing some of those concerns for the Latin America region: ISPE's 2012 Mid-Year meeting in Miami aimed to facilitate knowledge exchange among Latin American participants and with colleagues around the world; for the first time two pharmaco-epidemiology courses were presented in Spanish.

Generating energy

The courses comprised 22 topics ranging from general and basic pharmacoepidemiologic concepts to more sophisticated methods. Introductory courses were presented in English by Tobias Gerhard, Almut Winterstein, Soko Setoguchi and Syed Rizwanuddin Ahmad. The Spanish counterpart was presented by Maribel Salas, Sonia Hernandez-Diaz and Ariel Arias.

In the afternoon, the sun of Miami inspired attendees to continue with advanced courses: in English with Stephen Evans (Bayesian Methods), Samy Suissa (Time-Related Biases) and Til Stürmer (Confounding and Selection Bias); Susana Perez-Gutthann (Databases), Maribel Salas (Drug Utilization Measures), Sonia Hernandez-Diaz (Estimation of Drug Exposure), and Ariel Arias (Risk Management) in Spanish equivalents.

Participant reaction and the intellectual environment was positive and full of energy in the plenary session 'Pharmacoepidemiology in the Cloud' by Bram Hartzema, who encouraged the use of new technologies. The energy continued into the evening welcome

reception. The salsa background reminded us why the name of the society started with 'I' for International. The wine, cheese and bread whetted the appetite of conversation and exchange of ideas amongst participants.



The 'Formulary Development' session, from left: Albin Chaves Matamoros, Costa Rica; Luis Alesso, Argentina; Anthony Wong, Brazil; Luciane Lopes, Brazil; Pedro Rizo Rios, Mexico.

A region of change

Next day Pharmacoepidemiology in Latin America made clear that the region is changing economically and demographically, health care needs are increasing and people are demanding better systems, more trained health professionals and more government involvement to develop pharmaco-epidemiology and pharmacovigilance. There are barriers that need to be eliminated, and organizations like ISPE, ISoP, WHO, PAHO and others have a key role. Presentations described the Mexican (Pedro Rizo Rios) and Costa Rican (Albin Chavez Matamoros) initiatives to improve pharmacovigilance systems and challenges to carry out research in the region (Veronika Wirtz).

ISPE President Nancy Santanello introduced the keynote Observational Studies of Drug Effect as Evidence for Randomized Trials: Samy Suissa described the role of immortal time bias using examples of published articles and potential solutions for time-related biases. He received a standing ovation and the recognition of ISPE. Robert Reynolds and Chris Delaney moderated the database development session where Development of Patient Registries (Nancy Dreyer), Database Development (Andrew Maguire), and Distributed Practice Networks (Veronika Wirtz) reminded us of the importance of appropriate design and implementation of registries, and considerations in the development of databases for research.

Formulary Development in the Americas heard how governments developed drug formularies in Mexico (Pedro Rizo Rios), Costa

Rica (Albin Chavez Matamoros) and Brazil (Luciane Lopes). Although the processes are different, the need for more local data to make informed decisions is something all share. That message was followed by The Synthesis of Information of Observational Data for Decision Makers with discussion of heterogeneity meta-analysis of observational data with low event heterogeneity (Jon Shuster), as an opportunity and limitation to the interpretability of meta-analysis of observational studies (Jesse Berlin), statistical sophisticated methods for meta-analysis of observational data (Stephen Evans) and utilization of meta-analysis of observational data in the paradigm of drug safety in the FDA (Tarek Hamad). The scientific sessions closed with a session on data analysis of data visualization moderated by Elizabeth Andrews, where opportunities for exploratory visualization in observational data analytics (Patrick Ryan), statistical visualization of method summary (Xiaochun Li) and novel visualization approaches in safety surveillance (Andrew Bate) were discussed.

The day was summarized by Maribel Salas and Bram Hartzema with the presentation Atando Cabos (Tying ends), which integrated the main messages discussed and encouraged ISPE members to increase collaborations among members and also with other regions. Finally, Susana Perez-Gutthann, Chair of the Annual ISPE Meeting reminded us that the next scientific 'stop' will be Barcelona, Spain (August 23-26, 2012).



Nancy Santanello (ISPE Current President, FISPE, Merck) makes a presentation to Maribel Salas (AstraZeneca) as event co-chair.



Nancy Santanello presents to Abraham Hartzema (University of Florida) as co-chair.

Patient reporting at WHA

Hanna Lindroos

At a 'side event' during the 65th World Health Assembly (WHA) at the UN building in Geneva, the Monitoring Medicines project had the opportunity to present work done on empowering patients in pharmacovigilance by direct patient reporting.

how to empower patients in pharmacovigilance.

Shanthi Pal (WHO) discussed the role of the WHO. The current focus is too much on adverse *drug* reactions and *medicine* safety

vigilance systems and helping to remedy under-reporting.

The representatives from patient organizations – Regina Kamoga from CHAIN in Uganda, Svilen Konov from the European AIDS treatment group and Henrik Arildsen from HIV Europe – all agreed that there is a need to empower patients, because when things go wrong it is they who suffer the harm. A direct patient reporting system could improve the number of reports coming in as long as the reporting tool is designed in a way that patients are comfortable with, using language they can understand.



The Monitoring Medicines WHA side event on direct patient reporting

Empowering patients

Currently, in most countries only health practitioners are encouraged or required to report adverse drug reactions and other medicine-related events to health authorities. Under-reporting is widespread. Enabling and encouraging reporting directly from patients can address several shortcomings in current pharmacovigilance and healthcare systems. These issues were explained by several knowledgeable speakers from project partners and patient organizations invited to participate at the WHA seminar and to share their views on

when it should be on patients and their safety. The question is whether pharmacovigilance can become more patient centred and if so, how?

Scrutinizing the pioneers

As part of the Monitoring Medicines project, Florence van Hunsel from the Netherlands pharmacovigilance centre has studied patient reporting in the pioneer countries already accepting direct patient reports. The conclusion is that direct patient reporting contributes greatly to signal detection, covering the blind spots in the pharmaco-

Finally, Jesper Kjaer from Copenhagen HIV programme introduced an online resource developed for healthcare professionals in the HIV field. The resource contains the latest information on the side effects of anti-retrovirals, easy to understand articles, links to relevant presentations and a risk evaluation tool.

The seminar presented several views supporting direct patient reporting. All participants agreed that direct patient reporting could provide valuable information when analyzing adverse drug reactions and that an accessible tool would help alleviate under-reporting.

Pharmacovigilance in TB Programmes

A practical handbook on the pharmacovigilance of medicines used in the treatment of tuberculosis – Enhancing the safety of the TB patient was recently published by WHO. It can be downloaded from the WHO web site www.who.int/medicines/publications/pharmacovigilance_tb/en/.

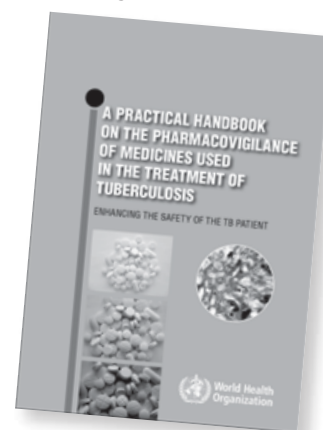
David Coulter from New Zealand prepared the first draft of this handbook and Geraldine Hill, also from New Zealand, re-worked a number of Annexes. The text underwent further editing by WHO colleagues, and was

presented to the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) at its various stages of development.

This handbook was produced with financial support from the European Commission under its Seventh Framework Programme (FP7), as a deliverable of the FP7 'Monitoring Medicines' Project.

This is the third in a series of WHO handbooks on pharmacovigilance in major public health programmes. The first, describing pharmacovigilance in malaria treatment programmes, was published in 2008. The second, focusing on drug safety issues of antiretroviral medicines, became available in 2009. David

Coulter has been the main author of all three publications and we are all greatly indebted to him for his diligent work.



Catch them young

S Manikandan & G Sivagnanam

Voluntary reporting of adverse drug reactions (ADRs) is the backbone of pharmacovigilance. The Pharmacovigilance Programme of India aims to foster the culture of voluntary reporting by healthcare professionals. Like any habit, it is advisable to inculcate the habit of voluntary ADR reporting at a young age. Hence, the need to report and how to report ADRs should be impressed upon medical students right from the formative years in their profession.

Unconventional learning experiences can augment the efforts to nurture these habits. The Department of Pharmacology, Indira Gandhi Medical College & Research Institute, Puducherry, India conducted an 'Intercollegiate Collage and Crossword Competition' on 31 March 2012 for medical undergraduates. Around 100 students from various medical colleges in Puducherry and the neighbouring states participated in the collage competition. In teams of two, students were asked to prepare a collage on the theme 'ADR Monitoring & Reporting'.

All the teams took part actively and the event showcased the extraordinary creativity of the students. The prepared collages illustrated the ill effects of ADRs, highlighted the need for ADR monitoring and explained the ways to report them. All these collages were displayed and everyone (both students and faculty) was excited to view them. This exhibition helped to emphasise the need for ADR monitoring and reporting not only amongst students who participated in the competition but also their peers. All felt that this was a pleasant and novel way to create awareness about pharmacovigilance.

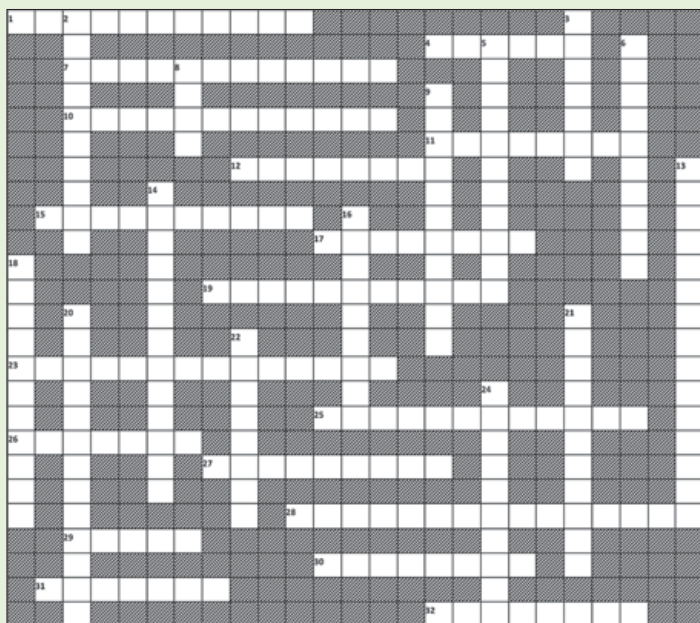
The event didn't stop there. An ADR crossword puzzle competition was also organised in which nearly 200 students participated. They were thrilled to solve the puzzle which had interesting clues with anagram, double meaning clues and cryptic clues. A debriefing session for the puzzle was also held after the competition. The feedback from the participants revealed that such



Students at the Intercollegiate Collage Competition

competitions helped them a lot in improving their knowledge, attitude and practice of ADR monitoring and reporting. These events indicate that when it comes to change in attitude and practice, the golden rule remains 'Catch them young'.

ADR Crossword Puzzle



Down

2. Iodide laden guy leaves his footprints in eye (10)
3. Hits the anucleated cells (7)
5. Neurotoxic spindle poison (11)
6. Blue or green, its the same with thy seduction (10)
8. Source of the hormone harming smokers (4)
9. Paradise lost, paradise regained (11)
13. Nasal decongestant and precursor for illicit methamphetamine (15)
14. Photophobic restrained in a red coffin spits cyanide (13)
16. May cause deafening diuresis (9)
18. Causes hypoglycemia followed by hyperglycemia (11)
20. Patch me at dawn; catch me at dusk (13)
21. Pope Marelix has sudden irresistible somnolence! (11)
22. Acronymous drug is atrocious to fetus (8)
24. Antihypertensive interfering with cross matching (10)

Solution on page 22



'Drug allergy'

'Let the drug cure not kill'

Across

1. 'Exam or lipid' cannot overcome aging (11)
4. Source increasing risk of HIT (6)
7. Analgesic that causes frontal headache (12)
10. Steals blood, but unlike Robin Hood (12)
11. Makes one mad as a hatter (8)
12. Sang the swan's song for the pop star (8)
15. Wakes up the sleeping Koch's (10)
17. Drops me down after the first gulp (8)
19. Novel kinetic properties make this inhaled steroid less risky (11)
23. Decreases acid but increases symptoms in gastric ulcer (14)
25. Cuddles the head; meddles the heart (12)
26. Couples the beat (7)
27. Oculomucocutaneous syndrome showed this drug the way out (9)
28. Relaxant that can make you hot (15)
29. St. Anthony extinguished its fire (5)
30. Blurs the vision like being in a snow storm (8)
31. Tiny drug troubles us with tremor (7)
32. FDA warning aboding on the carton (5,3)

Recipe for a successful system test

Ulrika Rydberg



Happy faces at the UMC office during the successful system tests of VigiFlow and the new Swissmedic gateway. In the picture are from left: Wolfgang Renftle, Ulrika Rydberg, Klas Östlund, André Voegelin, Guido Strack and from the back Monica Plöen.

Take one national pharmacovigilance centre with a drive to automate handling of Individual Case Safety Reports (ICSRs). Add a few market authorization holders (MAHs) that already use automated transmissions to send ICSRs to regulators. Stir in VigiFlow and a newly built gateway. Sprinkle with tension, minor problems and excitement to taste. Serve while hot.

This recipe was tested on 8 June when for the first time ICSRs in the E2B format were sent completely automatically between VigiFlow and the ICSR management systems of three MAHs. ICSRs were sent both from the MAHs to VigiFlow and from VigiFlow to the MAHs. The national centre receiving and sending is Swissmedic, the Swiss Agency for Therapeutic Products (see page 18, UR57). They have had a gateway built for this purpose and UMC has developed the connection to VigiFlow. When this will go live in November, Switzerland will be in the

technical forefront since they will be able to both receive and send ICSRs automatically.

Three visitors from Swissmedic were in Uppsala on 7–8 June for the tasting session: Wolfgang Renftle, Guido Strack and André Voegelin. The aim of their visit was to plan the continuing project for automatic transmissions of ICSRs and to discuss necessary changes in VigiFlow for the November 2012 release (see below). The successful system tests were the high point of this very fruitful visit.

Gateway

In this instance an electronic interchange gateway; a portal that allows transfer of electronic documents or business data between computer systems via a secure link.

e-Learning re-launch

Ulrika Rydberg

VigiFlow, the UMC's web-based Individual Case Safety Report (ICSR) management system, is specially designed for use by national pharmacovigilance centres in the WHO Programme for International Drug Monitoring. A web course teaching data entry in VigiFlow has been available since 2009. Unfortunately, several users experienced technical difficulties that made it impossible for them to take the course. To make it more accessible to all users it has now been moved to another technical platform. All users who have a user name and password for the course can still use these. Since the course has also been brought right up-to-date with the latest changes in VigiFlow, it might be worth a visit for those who did not encounter the technical difficulties the first time!

The VigiFlow e-Learning course is available on request to all new and old VigiFlow users; please contact vigiflow@who-umc.org if you wish to take the course.

Screenshot from the updated VigiFlow e-Learning course

Releases in 2012

VigiFlow version 4.3 was released in April 2012. This was a minor release and the changes mostly concerned import and export of E2B files and the submission manager in VigiFlow. An overview of these changes is given on the VigiFlow login page, and the Release Notes describing all changes can be downloaded from the VigiFlow User Group site on the UMC Collaboration Portal. The Release Notes can also be sent on request to those who do not have access to the User Group site.

In late November 2012, a bigger release is planned. The exact changes that will be included are not yet decided but the development has already started. One of the planned improvements is to the Excel export from the Report listing profile in the Search and Statistics module that many users have asked for. A proposed new version of this Excel export can be viewed and discussed at the VigiFlow User Group site on the UMC Collaboration Portal.

Visitors

Giuseppe Roberto



Giuseppe is a PhD student in the Doctoral School of Pharmacology at the University of Padova in northern Italy. Working with the Emilia-Romagna Regional Centre of Pharmacovigilance at the department of pharmacology of the University of Bologna, he is collaborating with the regional signal detection group for the post-marketing surveillance of vaccine safety. The coordinator of the signal detection activities at the Italian national centre of pharmacovigilance, Ugo Moretti, suggested that he apply for an internship at the UMC.

"I arrived in Uppsala in January to conduct a six-month research project entitled 'Disease-specific adverse event following immunization: characterization of a newly-described reporting bias through the analysis of VigiBase'. I have had the pleasure of working in the UMC Research Department, mainly under the supervision of the research pharmacist Johanna Strandell and vaccine specialist Jerry Labadie. The study is now finished and the relevant paper will be submitted for publication in the next few weeks.

I am very glad of my experience at the UMC. I had the opportunity to learn more about pharmacovigilance from some experienced people. I also found a very professional working environment where everyone is always friendly and helpful. Thanks to all the UMC staff."

Chinese delegation

On 23 April the UMC had the pleasure of receiving a high-level delegation from the State Food and Drug Administration (SFDA), Peoples Republic of China for a short visit. Head of delegation was Mr Shao Mingli, former commissioner of SFDA. Since the UMC Director was on a duty travel overseas the delegation was received by Sten Olsson and Annika Wallström. They provided an overview of UMC activities, partnerships and aspirations and gave a status report of the SFDA – UMC collaboration project that started by the signing of an agreement in Beijing in July 2011 (see also page 5 of UR54 and page 7 of this issue).



Mr Shao Mingli, Past Commissioner and Xu Youjun, Director General, Department of International Cooperation, SFDA

Looking out for threats

Michael Deats, Project Manager, WHO SSFFC* Monitoring Project, visited the UMC on 12 June to better understand the analytical methodology developed by a



Michael Deats

team in the UMC Research Department for identification of geographical and time limited clusters of reports of unexpected lack of efficacy in VigiBase. Such clusters can potentially be indicative of the presence of SSFFCs in the marketplace. Limited verification of the ability of the method to identify such product quality problems have been made within the Monitoring Medicines project but further field testing is warranted (see www.monitoringmedicines.org).

Michael Deats described to the UMC team how the WHO SSFFC Monitoring Project is trying to assemble relevant data from many different sources to enable tracing of the origin of the products that represent a major threat to patient safety, fair trade and public confidence in healthcare systems.

* Substandard/Spurious/Falsely-labelled/Falsified/Counterfeit medical products

Visitor from afar

On 20 June we welcomed Dhenili Perera for a short visit. Dhenili is currently on a three-month internship at the Essential Medicines and Pharmaceutical Policies department of WHO, working with validation of country information on WHO pharmaceutical



Dhenili Perera and Cecilia Biriell

indicators. When Dhenili is not a WHO intern she is a clinical pharmacist at Austin Hospital, Melbourne, Australia. After her visit to the UMC she promised to continue filling her adverse reaction reports very carefully before sending them to TGA, her national pharmacovigilance centre.

Meetings, bloody meetings

Bruce Hugman

A new version of the famous 1976 Video Arts training film, with its memorable title and hilarious content, starring John Cleese when he was a great deal younger and thinner, is about to be issued.¹ The message of 'manage meetings intelligently and effectively' is as important as ever.

During the recent UMC Training Course, we had a quick review of how much time participants in the communications module spend in meetings each week. Most said between three and ten hours per week; a few, more than that, and one, startlingly, between twenty and thirty hours per week.



Participants in the UMC Training Course Communications Module take a break on a sunny, spring day in Uppsala, after reflecting on their experience of unproductive meetings at work.

Reports from meetings in Ghana earlier this year suggest similar experience among pharmacists, academics and pharmacovigilance personnel in West Africa.

When asked whether time spent in meetings was felt to be productive, assessments varied from never to usually, with a most votes on the negative side (rarely, occasionally).

This was not a scientific survey, but the views expressed are similar to those you will hear if you ask any group of professionals, anywhere in the world: meetings, on the whole, are seen as sometimes useful and productive, but often distracting, demotivating and wasteful, and almost always too long.

Apart from the obvious professional and psychological costs, the 'elephant in the room' is, of course, the gigantic personnel cost: tens of millions of hours every day, in every kind of organisation, in every country in the world.² It seems to be the one area in which no one ever sees that enormous savings could be made.

Many meetings are conducted with a degree of amateurishness which is astonishing for the modern age, usually because of inexpert chairing, lack of clarity of purpose and lamentable time-management. Good chairing is a highly skilled activity. The default holders of the job (often the oldest or most senior personnel) aren't necessarily good at it.

Agendas often do not have clear objectives which justify gathering a bunch of people in the same room at the same time at all; and, maybe most damaging of all, many meetings don't have an agreed time-limit. Meetings will expand to fill the time available without proportionate benefits: a discussion which is allowed to ramble on for hours is unlikely to deliver better results than a well-disciplined, focussed discussion with a specific, agreed time-limit of (say) one hour.

There are immense resources on the internet for those who'd like to learn how to conduct better meetings. There seems to be an organisational taboo in many places on tackling this whole topic, partly because it's often tangled up with issues of authority, status and control. If we're looking for a trigger that might prompt thoughts of reform in even the most hardened meeting-addicted manager, then the financial cost of meetings seems a good place to start, even when the human cost is not taken seriously. A further radical and productive question is, of course, "Is this meeting actually necessary at all?"

1. Video Arts, *Meetings Bloody Meetings and More Bloody Meetings*; www.videoarts.com
2. For example: 'Meetings dominate business life in America today. According to the National Statistics Council, 37 percent of employee time is spent in meetings. Other data indicate there are 11 million business meetings each and every day.' Sourced at: www.verizonbusiness.com

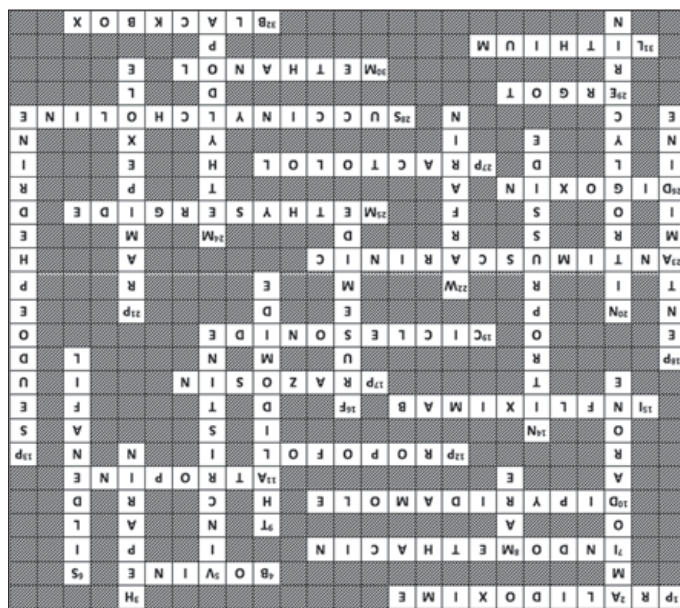
EMA consultation

The European Medicines Agency continues to make progress with modules of the guideline on Good Pharmacovigilance Practices (GVP). Two new modules have been released for public consultation until 24th August 2012. Full details may be found on the EMA website (www.ema.europa.eu/ema/ > News).

GVP is a set of measures drawn up to facilitate pharmacovigilance within the European Union (EU) which apply to marketing-authorisation holders and medicines regulatory authorities in EU.

Staff news

Over the last quarter we have said goodbye to four members of staff who are moving on: Annica Flygar, Johan Hopstadius, Gunnar Dahlberg and Andreas Zetterström. We wish them all well in the future.



Crossword Solution

DATES	TITLE	PLACE	ORGANISER/CONTACT
13-15 August 2012	Pragmatic Approaches to Drug Safety Across the Premarketing and Postmarketing Continuum	Horsham, PA, USA	DIA Tel: +1 215 442 6135 E-mail: Marilyn.Ginsberg@diahome.org
23-26 August 2012	28 th International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Barcelona, Spain	ISPE www.pharmacoepi.org/meetings/ E-mail: ISPE@paimgmt.com
5-6 September 2012	Back to Basics in Pharmacovigilance	Fareham, UK	Drug Safety Research Unit Tel: +44 (0)23 8040 8621 www.dsru.org/trainingcourses E-mail: jan.phillips@dsru.org
18-19 September 2012	3 rd Annual Pharmacovigilance Asia 2012	Singapore	IQPC Worldwide Pte Ltd www.pharmacovigilanceasia.com/
17-28 September 2012	Cours Francophone Inter Pays de Pharmacovigilance	Rabat, Morocco	Centre Anti Poison et de Pharmacovigilance du Maroc Tel: +212 537 77717467; Fax: +212 537 77717479 E-mail: rsoulaymani@gmail.com
19-20 September 2012	Critical Appraisal of Medical and Scientific Papers: How to read between the lines	Southampton, UK	Drug Safety Research Unit (details as above)
20-21 September 2012	Pacific Drug Safety Summit	San Francisco, USA	BioSoteria, Inc. http://www.pacificdrugssafetysummit.com/
24 September 2012	Essential Guide to Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 730008 www.management-forum.co.uk E-mail: registrations@management-forum.co.uk
1-3 October 2012	International Conference and Exhibition on Pharmacovigilance and Clinical Trials	Chicago, USA	OMICS Group Conferences Tel: +1-650-268-9744; Fax: +1-650-618-1414 E-mail: pharmacovigilance2012@omicsonline.org -or- pharmacovigilance2012@omicsgroup.com www.omicsonline.org
3-8 October 2012	FIP Centennial Congress (includes 'Creating a future of better pharmacovigilance' / information sessions)	Amsterdam, Netherlands	FIP www.fip.org/amsterdam2012/
17-18 October 2012	Risk Benefit Assessment in Pharmacovigilance	Fareham, UK	Drug Safety Research Unit (details as above)
24-25 October 2012	Case Narrative Writing for Reporting Adverse Events	Fareham, UK	Drug Safety Research Unit (details as above)
26-28 October 2012	7 th Asian Conference on Pharmacoepidemiology	Bangalore, India	ISPE www.acpe-india.org/
30 October - 2 November 2012	12 th ISoP Annual Meeting	Cancún, Mexico	International Society of Pharmacovigilance www.isop2012.org
23-25 November 2012	12 th Annual conference of SOPI	Ghaziabad, India	Society of Pharmacovigilance India
11-13 April 2013	ISPE Mid-Year Meeting	Munich, Germany	ISPE www.pharmacoepi.org/meetings/ E-mail: ISPE@paimgmt.com

6^{ème} Cours Francophone Inter Pays de Pharmacovigilance

17-28 Septembre 2012, Rabat, Morocco

This French language course runs in ten successive modules:

I Problématique des effets indésirables des médicaments

II Organisation de la pharmacovigilance

III Notification : conception et promotion

IV Evaluation de la relation de cause a effet : imputabilité

V VigiFlow

VI Gestion du risque, VII Effets indésirables spécifiques

VIII Feedback, indicateurs de suivi, rapports,

IX Champs d'application de la pharmacovigilance,

X Plan d'action pour le développement de la pharmacovigilance

For more information go to the website: www.capm.ma/ and follow the links.



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.

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About UMC > UMC staff – on our website.

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