

MUR63



WHO in Rome | Reporting news | Pharmacogenetics

UMC research | Compounding medicines for children



Marie Lindquist
Director
Uppsala Monitoring
Centre

The annual meeting of representatives of national pharmacovigilance centres participating in the WHO International Drug Monitoring Programme took place recently in Rome, Italy. How good it was to meet old and new colleagues and friends coming from all corners of the world; and what a wonder to walk past Fontana di Trevi on my way to the conference centre every morning!

There were many interesting topics on the agenda, but one presentation in particular has lingered in my mind. A colleague from Nigeria, Dr E.O. Okoro, presented research that confirms previous studies showing that cardiovascular morbidity and mortality in Nigerians with type 2 diabetes results mainly from uncontrolled blood pressure and not from atherosclerosis and elevated cholesterol. Therefore he questioned the strategy of lowering cholesterol as a universal treatment priority for the reduction of cardiovascular mortality in this population. Considering also the cost of statins (NGN220, as compared with NGN1 for thiazides), a cost which is largely borne by the patients themselves, he expressed concern about the aggressive marketing of statins now taking place.

I think the above is a vivid illustration that the concepts of rational drug use¹ and good pharmacovigilance practices must be linked. In a case like this, we could end up spending a lot of effort monitoring and analysing adverse effects of a drug, whilst not addressing the fundamental problem – that the basic principles of rational drug use were ignored and that the drug should not have been used in this patient in the first place.

I am firm in my belief that we cannot work in isolation from healthcare practice if we want to ensure patient safety. In my view, pharmacovigilance starts and ends with a patient. Therefore, pharmacovigilance must be an integral part of a quality management system spanning the whole cycle of healthcare delivery and patient care. This includes making the diagnosis; the choice of treatment; the processes of prescription, dispensing, administration; and outcome assessment. The outcome assessment should include an evaluation of the benefits of the treatment as well as monitoring for, examining, and managing patient harm. There has to be a continuing evaluation of all these activities and their results, with corrective measures implemented where necessary.

¹ "Patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community." WHO, 1985.

It particularly saddens me when the concept of 'pharmacovigilance' is reduced to denote the process of reporting itself, without much consideration of what needs to be achieved. With this mindset, pharmacovigilance risks becoming just a bureaucratic exercise, the most important feature of which can be seen to uphold a high level of market authorisation holder (MAH) compliance in sending ICSRs to the relevant authorities within the stipulated time frame. The notion that the term pharmacovigilance is commonly used in this narrow sense was supported by another colleague attending the Rome meeting. He said that he does not use the word pharmacovigilance when he teaches students, because their frame of mind would be tainted; to not lose their interest from the outset, he talks instead about diagnosis and management of iatrogenic disease.

*It should be pointed out that the view of pharmacovigilance as 'report shuffling' is **not** supported in current pharmacovigilance legislation, where such exists; on the contrary. The difficulty is, as always, to put the good intentions in regulations, directives and guidelines into practice. We need to raise our eyes from where we are now, and what we do now, to have a real impact on the lives and safety of millions of patients out there. We need to seriously consider: what are the best ways in which we can help health professionals and patients to make better therapeutic decisions; how we can influence decision makers and donors to put patient safety on top of their agendas; and how we can establish partnerships and collaborations to develop the tools and systems that are needed for good pharmacovigilance practice to become a reality. We must engage with all stakeholders, and coordinate agendas with those sharing the same vision, so we can avoid unnecessary competition for resources and wasteful duplication of work.*

Lack of resources for pharmacovigilance is a serious problem, but, as Dr Okoro and his colleagues have demonstrated, much can be achieved with the right mindset and determination to focus efforts where they have the best effect. Let's follow their good example!

A handwritten signature in dark ink, appearing to read 'Marie Lindquist'.

FEATURES

6-7

WHO database trends

8

Reporting compounding-related ADEs

10

Genetics and paediatrics

12-13

WHO Programme annual meeting in Rome

14

Unmasking research

15,19

Further education

REGULARS

2

Director's Message

4-5, 9,11

News from Around the World

16-18

Conference reports

20-21

New UMC publications

22

News from Bredgränd

23

Courses and conferences



Spreading safety

New developments and new WHO Programme members in Africa

Pharmacogenetics and children

Looking to prevent ADRs by identifying predictive genomic markers for specific ADRs



Rome

Large WHO Programme meeting in Italy captures spirit of global pharmacovigilance

Latest UMC research publications

Overview of six recent diverse papers involving UMC researchers



115 in the Programme

Sten Olsson

It has been a busy quarter for new full members entering the WHO Programme for International Drug Monitoring: numbers 113, 114 and 115 have joined.

Rwanda

In August the national pharmacovigilance centre of Rwanda, through VigiFlow, submitted its first batch of adverse drug reaction case reports to VigiBase. Rwanda became an Associate member in August 2010.

The Head of the national pharmacovigilance centre in Rwanda is:

Gladys Akimana
Pharmacovigilance Officer
Pharmacy / Ministry of Health
P.O. Box 84 Kigali – Rwanda
Tel: +250 788500348
E-mail: gladysak@gmail.com

Guinea

In early September two more countries joined the Programme. From the west coast of Africa, Guinea, an Associate since August 2009, again using VigiFlow, submitted its first adverse drug reaction case reports to VigiBase from the Ministry of Health and Public Hygiene of Guinea.

The Head of the national pharmacovigilance centre in Guinea is:

Kabiné Souare,
Directeur National
Direction Nationale de la Pharmacie et des
Laboratoires
BP 585 Conakry
Guinea
E-mail: Drsouare_kabine@yahoo.fr

Bolivia

A week later the national pharmacovigilance centre of Bolivia submitted its first batch of case reports to VigiBase. The Ministerio de Salud y Deportes of Bolivia had received Associate membership of the WHO Programme in March 2012, and again VigiFlow was used for report management.

Head of the national pharmacovigilance centre in Bolivia is:

Jenny Flores Toro
Unidad de Medicamentos y Tecnología en
Salud Ministerio de Salud y Deportes
La Paz
Bolivia (Plurinational State of)

Tel: + 541 2440122

E-mail: jflorestoro@hotmail.com

An Associate

From a different continent, an application was received at WHO from the Minister of Health, Professor Bounkong Syhavong on behalf of the Ministry of Health in Vientiane. The Lao People's Democratic Republic is now an Associate member of the WHO Programme for International Drug Monitoring.



EU states reporting to WHO

Priya Bahri

The European Medicines Agency issued a statement for participants at the WHO Programme annual meeting, held in Rome on 25-28 September 2013

Communication on reporting of adverse reactions occurring in the European Union to the World Health Organization
Update on the implementation of the EU pharmacovigilance legislation

The EU pharmacovigilance legislation adopted in 2010 requires the European Medicines Agency (EMA) to make available promptly all suspected adverse reaction reports that occurred in the European Union

(EU) to the World Health Organization (WHO).

De facto, this provision of reports should occur to the VigiBase database of the Uppsala Monitoring Centre (UMC), which acts as the WHO Collaborating Centre for International Drug Monitoring. While the legislation came into force on 1 July 2012, the new legal reporting provisions will only apply following release of successfully audited enhanced functionalities of EudraVigilance, the agency's web-based information system for the reporting, management and analysis of suspected adverse reaction reports.

The agency, in collaboration with the EU Member States and the UMC, has started its planning for the implementation of this legal provision, and the agency is working on the new functionalities for EudraVigilance.

In the interim, Competent Authorities in EU Member States continue reporting to the UMC in accordance with the guidelines on Good Pharmacovigilance Practices (GVP), module VI on the management and reporting of adverse reactions to medicinal products.

More information from [What's New > 27 September on the EMA website \(www.ema.europa.eu/ema/\)](#)

An hour in Reykjavik

Anette Sahlin and Helena Sköld

Although our main purpose in Iceland was vacation and sightseeing we had also made contact with Brynja Ásdís Einarsdóttir at the Icelandic pharmacovigilance centre and asked for a short visit.

On Vinlandsleid where the Icelandic Medicines Agency is located we got a warm welcome and were given a tour around the office before Brynja invited us to a meeting room where she gave a presentation of Iceland in general and Icelandic pharmacovigilance more in detail. As in many WHO Programme countries Iceland is struggling with a lack of resources in combination with a high level of ambition.

Helena Sköld then gave a short demonstration of the newly-launched Vigilize tool and I also took the opportunity to show the Vigimed discussion forum where members of the WHO Programme can discuss and share experiences at the UMC Collaboration Portal. We left Brynja and her colleagues after only one hour to allow them to continue with their important work, but we took away the feeling of welcome and camaraderie with us and that is still lasting now that we are back in our office.

We would recommend everyone to visit 'the country where continents meet' at least once in a lifetime.



Lyfjastofnun (Iceland medicines agency) offices in Reykjavik

US MedWatch programme turns 20

Sten Olsson



This year the MedWatch system for the reporting of problems related to medicines, medical devices, biologics, foods etc celebrates 20 years of existence.

MedWatch, maintained by the US Food and Drug Administration, invites both health care professionals and consumers to submit reports to Food and Drug Administration (FDA), when they find problems with products regulated by the agency. Over the years, most reports have been submitted by health care professionals but reports from consumers are getting more numerous.

FDA has introduced new web-based learning tools, MedWatchLearn to educate students, health care professionals and consumers how to properly fill in a MedWatch report. Currently MedWatch forms have to be faxed or mailed to FDA but on-line submission capability will soon be available.

RISK: What risk? Whose risk?

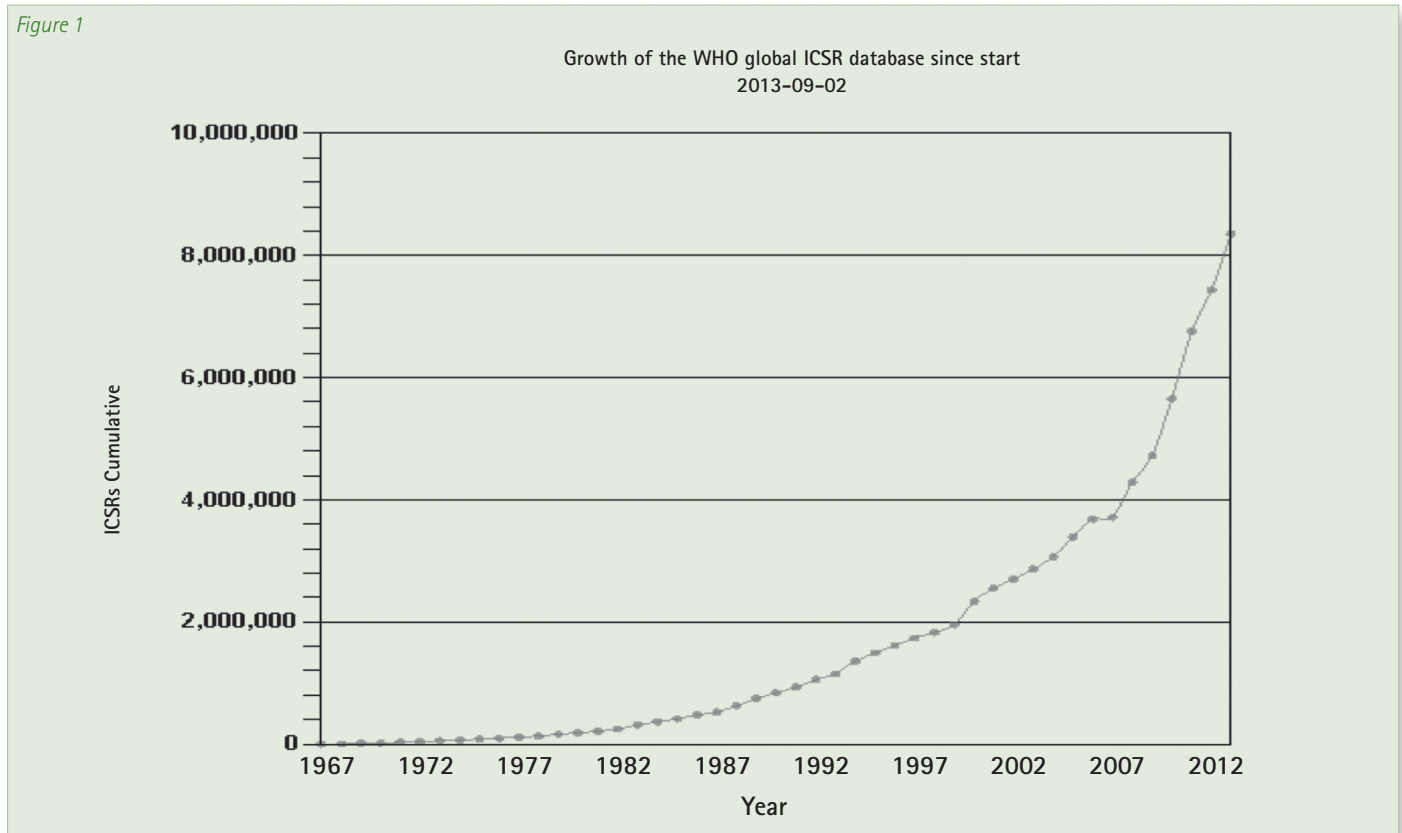
Save the date for Uppsala Monitoring Centre Research Conference 2014
May 22–23, Uppsala Concert and Congress Center, Uppsala, Sweden.
www.who-umc.org/research

Research
Conference
2014

VigiBase: stable growth

Sara-Lisa Fors

Figure 1



Twice a year a summary of the latest news and statistics on the reporting to the WHO Global Individual Case Safety Report (ICSR) database, VigiBase® is presented in Uppsala Reports. Some statistics can also be found on the UMC website via Pharmacovigilance > The WHO Programme > Reporting Trends.

VigiBase growth in last five years

At the time of writing, the WHO Global Individual Case Safety (ICSR) database, VigiBase, contains 8,358,814 ICSRs (see Figure 1). The rapid increase in the number of ICSRs lately has actually contributed to a doubling of the database in only five years. In other words, half of the data in the database has been entered during 2008 or later.

A minor part of the increase comes from new countries joining the WHO Programme. Today a total number of 115 countries have contributed with their ICSR data to VigiBase, the newest being Liberia, Rwanda, Guinea and the Plurinational State of Bolivia. However, most new countries, still having very young pharmacovigilance systems, collect only fractions of what the old members do, and hence the major part of the increased reporting actually originate from older members.

The top 10 contributors of ICSRs in VigiBase in a historical perspective remain the same as in the last update (UR61). These are all

countries with large populations and consequently they get many ICSRs. Eight of them are also in the top 20 list of reporting

Figure 2

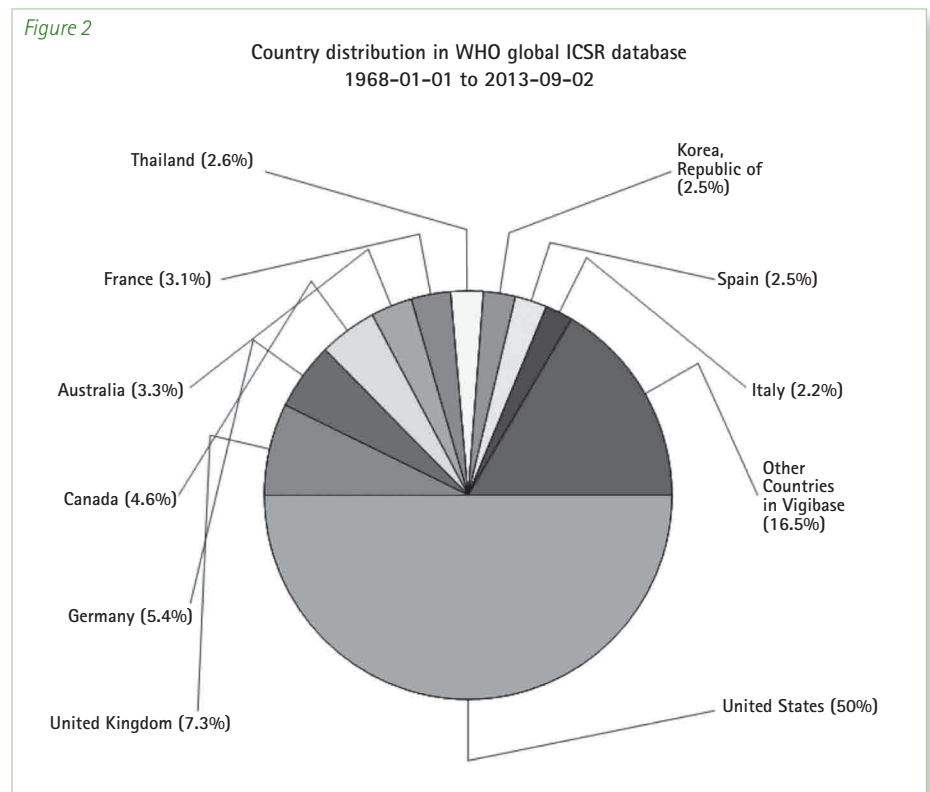
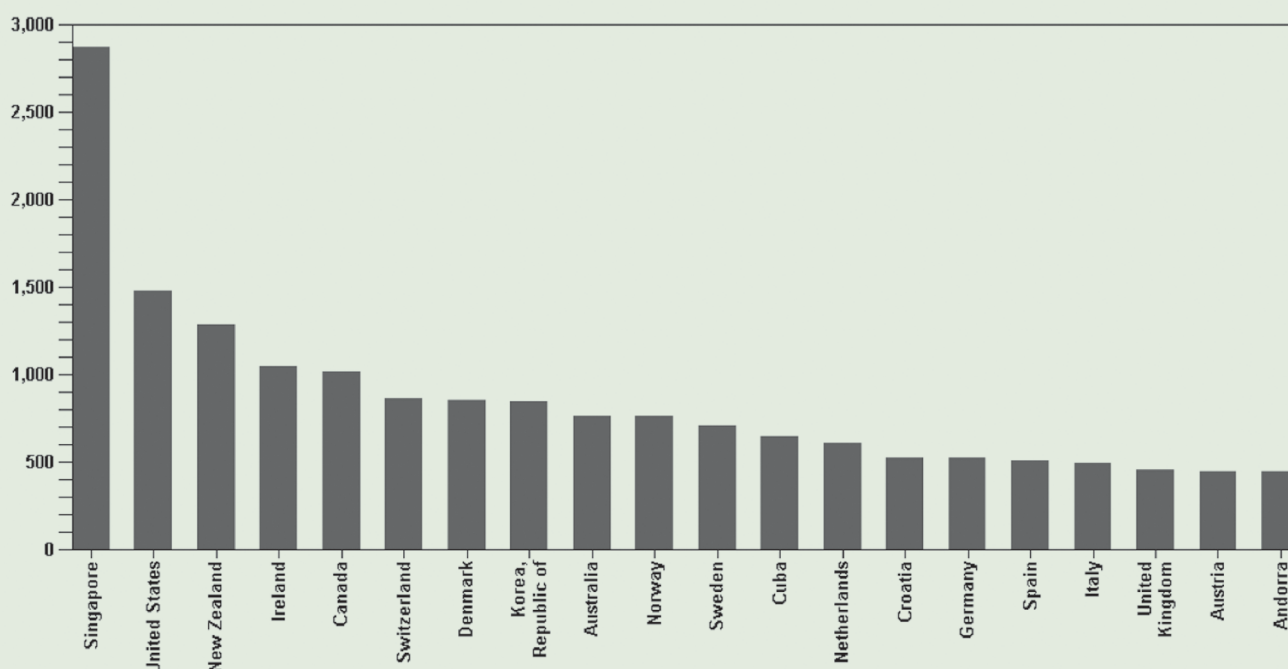


Figure 3

Active ICSRs in the WHO global ICSR database per million inhabitants and year
Period covers 2008-09-02 to 2013-09-02



rates per population during the last five years, showing that pharmacovigilance is well spread in that country (Figure 2).

The 'Reporting rates per population' graph (Figure 3) allows for a comparison of the reporting regardless of the size of the population. With Singapore still in the lead far ahead of US and New Zealand, and the rest of the countries the same as six month ago, this graph too remains stable, only the order of some countries has shifted around somewhat. If you are interested in a full list including all member countries, please contact vigibase@who-umc.org.

Renewed contributions

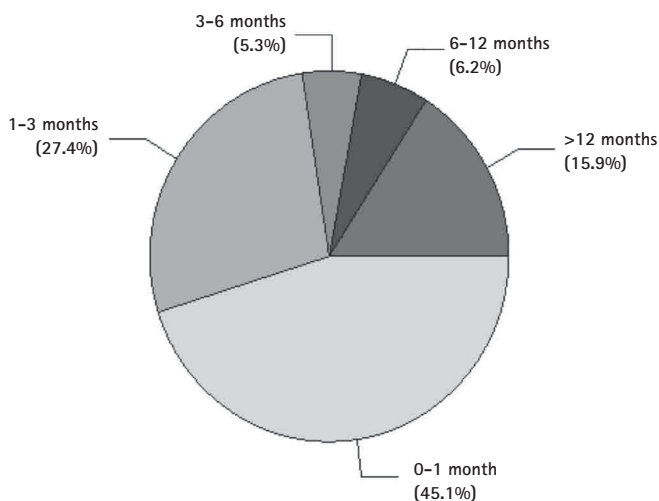
From time to time even older members get problems submitting ICSRs regularly. The reason is most often technical problems that appear, when for example changing database.

After some years with such technical problems, Egypt has now re-initiated their ICSR contribution to VigiBase. Earlier this year the Egyptian Pharmacovigilance centre decided to use VigiFlow as their national ICSR management system, which also solved the issue of submitting ICSR data to VigiBase in the correct format.

Chinese contributions have also recently been re-initiated. In August SFDA submitted a test file for entering in VigiBase. Validation of the test file is currently on-going and we

Figure 4

Time elapsed since last submission
2013-09-02



expect new Chinese ICSRs to be found in VigiBase in a near future.

Submission frequency

To ensure that the database is kept up-to-date, members of the WHO Programme are expected to actively contribute their ICSRs to VigiBase, that is, preferably more often than once a month but at least every quarter. Regrettably, an increasing number of countries have not submitted any ICSRs during the past 12 months, compared to the

last statistics update. On the other hand, this is still a small fraction of the countries compared to those that actually do submit ICSRs according to the submission criteria. More than 80 countries, from all corners of the world, are *actively* contributing to a useful and up-to-date database.

Compounding related adverse drug events – the case for reporting

David Woods

Consider the following scenarios;

A child prescribed phenobarbitone syrup which had to be compounded from tablets becomes comatose after the "correct dose" was given.

A pharmacist uses a different brand of amiodarone tablets to compound a suspension for a child. The carers return after several weeks complaining that the suspension is too thick to measure and they have stopped giving it to their child.

An infant discharged from hospital receives diazoxide from a community pharmacy after receiving the same drug in hospital. Within a few doses he child becomes dangerously hyperglycaemic.

An infant is given their usual dose of flecainide suspension compounded from tablets, and a few days after being given doses at home experiences a potentially life-threatening ventricular tachycardia.

As a practitioner I have personally encountered these events and in the case of diazoxide and flecainide, there are similar reports in the published literature. All of these situations could have resulted in a serious or even fatal outcome. Some of these events may be reported as an adverse drug reaction or even simply attributed to a complication of the underlying disease or other reason.

How likely is it that these events would be associated with a problem related to compounding the preparation, and even so, how likely is it that this would be reported?

Compounding is a common practice

Before considering what happened in these cases it is important to briefly consider the background to the problem. It is well recognised that pharmacists and sometimes nursing staff have to compound oral liquids using crushed tablets suspended in a vehicle. Such use occurs predominantly in children where an age-appropriate commercial preparation is either not available nor accessible in the market. This 'unlicensed use' of formulations is widespread and the risks to children are exacerbated by the fact that many of these medicines are also being used for 'off-label' indications. Many studies

have shown a high prevalence of this practice in well-resourced hospitals in developed countries, but the situation is even worse in resource-poor settings, with limited access to medicines and formulation ingredients.

Compounding oral liquids is risky

The expectation from this practice is that modifying a formulation by crushing a tablet and mixing it with a vehicle (often syrup or similar) will result in an effective and safe dose form that will be chemically and physically stable for the period it is prescribed for. In many cases these expectations are presumably met because the drug has the intended effect.

However, there are few, if any, clinical trials to prove this. Pharmacists are usually aware of the risks of compounding but there is often no alternative and availability of information is scarce. It is generally assumed that compounding provides a safe, reliable dose, but in many cases this assumption is flawed. Risks include chemical degradation, microbial contamination, toxicity due to an excipient or formulation component, precipitation of drug from solution, and formation of a suspension from which it is not easy to give a reliable and reproducible dose. These formulations are not subjected to rigorous industry standards and most are never tested at all.

If we return to the above cases; phenobarbitone was prepared using the sodium salt to give a solution, but due to a pH change (adding a flavour) free phenobarbitone precipitated and a large dose of insoluble drug was given. The amiodarone case is typical of the situation when a suspension works well with one brand of tablet but use of an alternative brand leads to physical instability making it unusable. The diazoxide example was a result of a change of formulation strength, a 50 mg/mL suspension was prepared instead of 5 mg/mL; the use of non-standard strength compounded liquids increases the potential for error and overdose. Finally, in the case of flecainide the preparation was originally a solution of the drug providing a reliable measured dose. In a period of hot weather the liquid was placed in a refrigerator and precipitation of flecainide occurred causing a concentrated dose to settle to the bottom of the container.



David Woods

Increasing awareness and reporting

If we increase the education of practitioners about these potential problems and create a mechanism to report these events I believe there would be several benefits:

1. It would increase general awareness of the problems and give an idea of the scale of the issue globally and the challenges faced
2. It would inform strategies for prevention of potentially harmful events
3. It would provide evidence and support for practitioners to lobby for support for better practices and better access to safer, age-appropriate medicines.

Designing the mechanism and deciding how and what to report is hopefully the next stage in the discussion.

David Woods is a consultant pharmacist with a special interest in medicines formulation for children. He is also the editorial director of the New Zealand Medicines Formulary.

Note: the author has only considered and given examples in the context of paediatric oral medicines. Any reporting would cover compounding in general including IV admixtures.

Ex-President of Ghana visits UMC

Antonio Mastroianni

Raising the profile of Neglected Tropical Diseases

Ex-President of Ghana, His Excellency John Agyekum Kufuor, found time during a visit to Sweden to visit the Uppsala Monitoring Centre (UMC) on 2nd September. After discussions with senior managers he gave a speech to staff on 'The fight against Neglected Tropical Diseases and Non-Communicable Diseases: the critical role of safe medicines'.

Hearing directly from a world leader was empowering for the UMC staff as President Kufuor stressed the importance of getting scientists and doctors to communicate with decision-makers in a way they can understand so that the hard work of science can be applied through effective pharmacovigilance policies.

President John A. Kufuor is the Global Ambassador of the Partnership for Neglected Tropical Diseases and Chairman of the John A. Kufuor Foundation whose mission is to improve leadership, governance and development across Africa. As a former Chairman of the African Union as well as Board member of several global initiatives in health and agriculture, his words carry much

significance in an increasingly active and multidisciplinary field.

Increasing interest

The World Health Assembly in Geneva adopted a resolution on all 17 neglected tropical diseases on 27 May 2013. The resolution urged Member States to "expand and implement interventions and advocate for predictable, long-term international financing for activities related to control and capacity", as well as calling for integration of such programmes into primary health-care services and existing public health programmes. These diseases, which affect over one billion people, are known to seriously impede development.

Supporting countries, programmes

The WHO Programme for International Drug Monitoring has begun to take an interest in the issue of Neglected Tropical Diseases at its annual meetings, and the UMC, with its key role in the WHO Programme, has a well-developed and tested technical capability to support countries and programmes in the management of adverse event data. The UMC's recent work in the area includes involvement in public health programmes in



John A. Kufuor talks to assembled UMC staff, with UMC Director Marie Lindquist (left)

Eastern Europe and Africa, and the UMC provides support for on-line data management tools and promotion of safety monitoring within disease programmes.

As Chair of Sanitation and Water for All (SWA) partners, President John A. Kufuor went on to take part in the high-level discussions at the Stockholm Water Week 2013.

New CIOMS working group on vaccine safety

Sten Olsson

CIOMS (Council for International Organizations of Medical Sciences), based in Geneva has a long track record. It has been instrumental in providing a platform for discussion and interaction between public and private sectors in areas such as safety monitoring of pharmaceuticals.

This year a new Working Group has been established as a support for the Global Vaccine Safety Blueprint and its implementation plan, the Global Vaccine Safety Initiative (GVSII). The aim is to assist low- and middle-income countries in their work with vaccine safety surveillance. The Working Group had its first

meeting in London on 29–30 May, 2013 and convened a second time in Geneva on 17–18 September.

The main objectives of the Working Group are to:

- promote a more efficient and rapid collection and exchange of information between national regulatory agencies, multilateral agencies and vaccine manufacturers
- develop and endorse harmonized tools and methods for vaccine safety monitoring activities between national regulatory agencies, multilateral agencies and vaccine manufacturers
- propose mechanisms for vaccine safety monitoring in difficult settings, i.e. those with minimal infrastructure.

The Working Group expects to be able to produce a consensus publication and/or guides in approximately two to three years.



Members of the new international CIOMS vaccines group in Geneva.

Genetic markers as risk indicators for ADRs in paediatrics

Bruce Carleton

The consequences for patients who experience severe adverse drug reactions (ADRs) are catastrophic. While some ADRs result in death, others lead to permanent disability, treatment cessation, or reduced medication compliance. Drug-induced harm is a global phenomenon that must be addressed.

Post-marketing evaluation

In order to optimally protect patients from drug harm, early detection and assessment of ADRs is critical. This includes determining the frequency and severity, the relationship to dose and duration of therapy, as well as the evaluation of patient factors that increase the risk. It is now apparent that genetics plays a much larger role to heterogeneous response than previously thought, or perhaps it is just that we now have the technology to assess the contribution that human genetic variation makes to drug response.

Active clinical surveillance

In 2005 the Canadian Pharmacogenomics Network for Drug Safety (CPNDS) established a national network of trained ADR surveillance clinicians in 13 paediatric academic health centres. Since then, CPNDS has expanded into the adult population and has established new surveillance sites at 13 adult academic health centres, also in Canada. From 2010 onwards expansion has begun internationally, with sites established in Mexico, the United States of America, and additional sites being set up in Africa, Switzerland and the Netherlands.

Active ADR surveillance networks can be effective strategies for both complete ADR reporting and drug safety biomarker research. The Network was designed to capture a broad range of ADR cases and target the surveillance of specific drugs or ADRs of principal concern. Clinicians who conduct surveillance are highly qualified and employed by the Network to identify children who have suffered ADRs and find matched controls from inpatient, outpatient and emergency departments at academic health centres in Canada. As of June 2013, 6,200 ADR cases and 56,385 matched controls have been enrolled.

Bedside-to-bench-to-bedside

This pharmacogenomics network characterizes ADRs in children and finds genomic solutions to the lack of predictability of many severe reactions. We have identified relevant biomarkers for three serious ADRs: anthracycline-induced cardiotoxicity, cisplatin-induced hearing loss and codeine-induced infant and toddler mortality. On-going studies include vincristine-induced peripheral neuropathy, drug-induced Stevens-Johnson syndrome and others.

The goal of CPNDS is to prevent ADRs in children and adults by identifying predictive genomic markers for specific ADRs. This includes incorporating these markers into diagnostic tools that will be used to predict and prevent ADRs through specific therapeutic recommendations based on an individual's genetic profile. Uncovering which drugs cause harm and detailed information about patient experiences are helpful, but most helpful in clinical care is finding determinants of why this occurs, so that alternative dosing or therapeutic strategies can be used. Since drug biotransformation is controlled by genes which are part of our natural ancestry, knowing which genetic determinants are responsible can improve the health and well-being of patients throughout the world.

Accessible pharmacogenetics

Clinical practice guidelines for pharmacogenetic testing are urgently needed for clinical care. We are developing rigorous and practical guidelines to allow clinicians to make better informed choices about drug therapy for patients. We have started this process by developing clinical practice guidelines for six drugs: cisplatin, anthracyclines, carbamazepine, warfarin,

codeine and tamoxifen. Several of these guidelines have been submitted for publication and others will be submitted in the next few months.

Bridging the gap

We are now piloting a Pharmacogenetic ADR Prevention Program in British Columbia, Canada. This two-year project will help us further understand how best to use genetic markers to improve the safe use of drugs in patients. We are beginning our work with two pharmacogenetic tests designed to predict cisplatin-induced hearing loss and anthracycline-induced cardiotoxicity. We are studying how the test results are utilized and understood by both clinicians and patients, before and after testing. We are evaluating the economic burden of these ADRs and the cost-effectiveness of the pharmacogenetic tests.

We recently published a case of a severely disabled child without the ability to communicate verbally. She was exhibiting signs of significant pain and irritability despite use of an appropriate dose of paracetamol and codeine. Genotyping revealed she was a codeine poor metabolizer, which allowed us to develop a better pain management regimen more suitable to her individual metabolic profile. The opportunities afforded by pharmacogenomics coupled with proper pharmaceutical care (i.e., through the establishment of a *priori* therapeutic objectives and monitoring for both drug effectiveness and harm at pre-established time intervals) can revolutionize the safe and effective use of medication in ways previously not possible.

A problem that needs attention

Drug-induced harm is a public health problem that deserves special attention. Pharmacogenomics promises a clearer path to predicting in whom harm is most likely to occur. This is a major step forward in meeting the ultimate goal of not just defining the drug safety problems but finding solutions.

Bruce Carleton is Director, Pharmaceutical Outcomes Programme, BC Children's Hospital, Professor of Pediatrics, Medical Genetics, Pharmaceutical Sciences, Population & Public Health and Chair, Division of Translational Therapeutics, Department of Pediatrics, University of British Columbia.



Bruce Carleton (centre), with Kristina Star (left) and Hanna Lindroos (right) of the UMC

Out and about in Africa

Hagar Hilda Ampadu

The vibrant staff of UMC-Africa is leaving no stone unturned when it comes to advocacy for pharmacovigilance in Africa. This has led to some interesting and productive country visits and training during this past quarter.

Advisory role

Technical and professional advice and support is offered during our visits:

- training key staff at national pharmacovigilance centres on how to stimulate their national ADR reporting
- supporting countries in improving their ADR reporting form design
- assisting them on how to handle ADR reports
- providing instruction and advocating the use of E2B compliant systems
- providing advocacy to their ministry of health to enable sustainable pharmacovigilance systems.

Programme membership

UMC-A undertook visits to several Associate member countries to support them to

become full members of the WHO Programme and to assist existing full members to strengthen their pharmacovigilance activities. Following Liberia in April 2013, Rwanda became a full member of the WHO programme in August followed swiftly by Guinea. Angola is in the process of applying for full member status.



UMC Africa training in action

With in-house capacity-building of staff, to open training being organized, the team is gradually making headway. The UMC-Africa is very passionate about empowering health professionals including pharmacists, doctors, nurses, and pharmacovigilance consultants, at regulatory authorities and national centres.

Specific training

For this reason, courses are also being organized on specific issues. ICSR reporting and management is one of the obstacles most African national centres face, and UMC-Africa is working hard to find solutions to these problems. The team is also working closely with pharma-industries, starting with Ghana, to increase the awareness of the need to report to the national centres.

All these exercises will continue and increase: 2013 is simply the start of superb relationship between Africa and pharmacovigilance. Kindly visit our website www.who-umcafrica.org for more updates.

Haemovigilance programme started in India

Sten Olsson

A haemovigilance programme was started in India in December 2012, built on the model of the pharmacovigilance programme which was initiated in 2010. The focus is on adverse experiences with blood transfusions and blood products.

Raising awareness

Currently 101 medical colleges, institutes, hospitals and blood banks are partners in the network which is coordinated by National Institute of Biologicals (NIB), at the Ministry of Health and Family Welfare, under the directorship of Dr Surinder Singh. Among the objectives of the programme are to create awareness about transfusion-related reactions among health care professionals and to collect evidence for regulatory decision making for CDSCO (Central Drugs Standard Control Organization, Ministry of Health and Family Welfare), the regulatory authority.

Web reporting

A specific web-based data management tool, Haemo-Vigil, was created by NIB and launched in January 2013 to facilitate reporting and data processing. An instruction

manual is also available online. Several continuing medical education courses have been run in different parts of the country. About 500 reports have been received so far. Recommendations from the programme will be shared with the national pharmacovigilance programme.

The target of the haemovigilance programme of India is to become a member of the International Haemovigilance Network by the end of 2014.

For more information see www.nib.gov.in

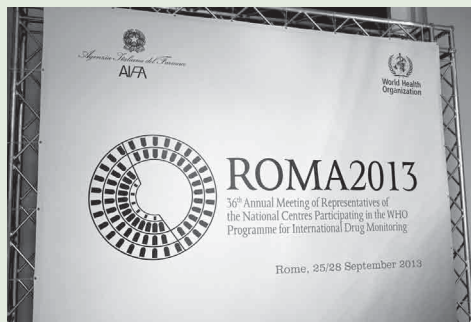


Dr Surinder Singh

Arrivederci Roma!

Geoffrey Bowring

There will be so many good reasons for visiting the Italian capital: the treasure trove of Roman monuments, the Renaissance art and architecture, and even food and shopping. For those working at national pharmacovigilance centres, an additional, important one presented itself in late September 2013: the 36th meeting of the WHO Programme for International Drug Monitoring. Remarkably, this annual pharmacovigilance meeting is now one of the largest of any WHO meeting in terms of countries and delegates.



Welcome to the WHO Programme meeting in Rome

Conviviality

Despite many new faces experiencing the meeting for the first time, the perennial spirit of international co-operation at these meetings – gradually getting larger over time – was soon rekindled. An important event at every national centres meeting is the Welcome Reception, the evening before the meeting commences. Rome possesses an ideal venue, the Nobile Collegio (Noble College) at the San Lorenzo in Miranda church overlooking the Roman Forum (sometimes referred to as the Temple of Antonino and Faustina). The College dates its mission of research and studies in pharmacology from 1430 and is still very active today.

Setting

The main conference venue was also conveniently situated in central Rome and perfectly configured for the activities of the WHO Programme's delegates: an amphitheatre as the plenary, with four rooms close by for the two sets of working group sessions.

Opening the database

After the opening ceremony, a major theme was confronted: UMC's Pia Caduff and Magnus Wallberg gave a dual presentation on making ICSR data available to the public. The 2002 WHO International Conference of Drug Regulatory Authorities (ICDRA) first explored the issue, and in 2008, national centres were asked to comment on proposals for public access to the WHO database. In 2011, ACSoMP (the WHO Advisory Committee on the Safety of Medicinal Products) recommended that access should be step-wise. For UMC to open VigiBase a new tool has been created based on application programming interface (API) coding.

Plenaries

Among plenary talks, Kees van Grootheest, former head of Lareb, now Professor of Pharmacovigilance at the University of Groningen in the Netherlands, gave a review of the scope of pharmacovigilance. He suggested that the well-known 2002 definition of pharmacovigilance was in need of updating to identify more specifically the drug-related responsibilities of our field. He urged for independence of pharmacovigilance within a culture of patient-centred decision-making and collaborative working. His final message was that pharmacovigilance should be viewed as a science and embedded in the academic setting, while working closely with related medical specialisms.

Dr Ernesto Jaramillo of the WHO Global TB Programme talked on approaches to the safety of medicines used in TB treatment. TB drugs may be used in combination with existing anti-TB drugs and others on an off-label basis,



Remains of the Forum



The opening ceremony; from left, Carmelo Pimpinella (AIFA), Ugo



Magnus Wallberg (UMC) leading the VigiFlow User Group



The excellent ma

creating a potential for previously unrecognised drug interactions and reinforcing the need for vigilance.

Giuseppe Pimpinella, Head of Pharmacovigilance at AIFA described the pharmacovigilance system in Italy, which has several unique features. He stressed some of the advantages of the Italian system, mainly related to an extra distance between the regulators and manufacturers, such as:

- targeted studies on aspects that would not be studied by pharmaceutical companies
- the study of rare ADRs or diseases, or small groups of patients
- less need for pharmacovigilance inspections.

Centres raise the issues

This year there was a record number of 'Problems of Current Interest' from national centre representatives – a total of 27 oral

presentations were made. Able chairing by Niamh Arthur (Ireland) and Rudolf Stoller (Switzerland) ensured that all were covered, with comments and questions, in the time available.

The wide range of subjects raised included misuse of benzydamine, pharmacovigilance inspections, fatal cases of IV administered perfluorocarbon for MRI, monitoring of artemisinin-based combination treatments, ADRs not related to the active substance, ADRs from Anti-MDR-TB drugs, natural rubber (latex) and risk of allergy or anaphylactic reactions, strabism reported after hexavalent vaccination, hallucinations after vaccinations, severe adverse reaction to black henna, Diane, gabapentin and hypoglycaemia and ferumoxytol and immediate type hypersensitivity reactions. Argentina, Brazil, Burkina Faso, Canada, Croatia, Eritrea, Italy, Morocco, Netherlands, Nigeria, Switzerland, Thailand and the UK all prepared cases to present.

Working Groups

Each year there are two sets of working groups where national centre representatives may discuss a variety of current topics for a couple of hours, and then make recommendations. Where relevant the matters discussed are taken further by WHO or its Collaborating Centres over the coming year(s).

2013's topics were:

- Pharmacovigilance centres supporting the work of quality surveillance systems
- Government commitment to pharmacovigilance
- National centre experiences with different systems for ICSR data management
- Herbal medicines
- Promoting safety monitoring of medicines in children
- Mass media and pharmacovigilance
- How sentinel sites and their networks can support pharmacovigilance
- Pharmacovigilance in curricula.

2014

At the end of the third day the Chinese medicines agency (CFDA) showed some slides to prepare and invite WHO Programme members to Beijing for the next meeting, in 2014.

Shanthi Pal thanked all those people who make the meeting possible. After an emotional closing ceremony it was farewell until the next time. But many will also return to the rich experiences of Rome, where pharmacovigilance is flourishing and the WHO Programme continued on its route to patient safety.



Shanthi Pal (WHO), Giuseppe Pimpinella (AIFA), Luca Pani (AIFA), and Moretti (Verona)



Ernesto Jaramillo (WHO) and Olena Matvieieva (Ukraine) in conversation



Meeting in meeting room



Evening social event outdoors

Detecting hidden signals

UMC Research Team refines automatic screening of data

Kristina Juhlin, Kristina Star, Niklas Norén, Xiaofei Ye

Making sense of enormous data-sets like VigiBase®, with more than eight million reports, requires very sophisticated software processes if potential signals of safety problems are not to be missed.

Since UMC developed its pioneering data-mining programme in 1998¹, processes have been constantly upgraded and improved. The detection of duplicate reports², the expansion of the methodology to cover drug interactions³ and signal detection in subgroups⁴ have made the process more and more refined, productive and reliable. Now, an algorithm for unmasking hidden adverse events has been added to the list of processes, after evaluation in both VigiBase and a smaller dataset from the Shanghai Signal Reporting System. It is useful and important for any organisation using automatic, electronic methods.

Extreme reporting

Disproportionality analysis is the primary, automatic method for reviewing large data sets for unusual and potentially important issues. This means that drug-ADR combinations that appear more frequently than expected are highlighted as being likely to represent safety issues that need expert manual review.

However, if a particular association is subject to extreme reporting rates, for example as the result of public controversy or media attention, this distorts the overall picture, pushing aside, or *masking*, other less prominent instances of concerns about the drug or the ADR. These masked associations may be of importance; now they are made visible through a process that discounts the effect of the disproportionately reported *outliers*.

Outlier removal: a simple unmasking strategy

Currently, around 25% of all safety reports in VigiBase on myocardial infarction as an ADR list the drug rofecoxib as the suspected cause (20,000/76,000). When using disproportionality analysis to identify other drugs that may cause myocardial infarction, this strong association will influence the analysis in a way that may hide other safety issues. This effect is referred to as masking and may delay or even prevent the detection of important safety issues (signals) from post-marketing surveillance.

The effect is most significant for adverse reactions for which a large proportion of the reports are on a single drug, such as the example of myocardial infarction and rofecoxib, while other ADRs remain largely unaffected. Among those most affected by masking are serious events such as myocardial infarction, rhabdomyolysis and hypoglycaemia.

An issue for attention

UMC researchers have developed a method that identifies the drug–adverse reaction combinations that distort the disproportionality analysis (referred to as *influential outliers*) and investigated if excluding reports on these combinations can improve signal detection analysis.

Results show that applying the unmasking method to VigiBase uncovered large numbers of previously hidden potential safety issues for the affected events. For myocardial infarction there was a 50% increase in the number of highlighted potential safety issues; for hypoglycaemia a 25% increase; for rhabdomyolysis several potential safety issues were highlighted that could have been detected one to two years earlier.

The research team's evaluation showed that the masking bias caused by extreme reporting rates on certain drug–adverse reaction combinations is a real issue that could affect patient safety by preventing or delaying the detection of serious adverse reactions that were reported but did not emerge through the automatic review process.

Pia Caduff, UMC's Chief Medical officer comments "UMC's automatic processes for screening large databases like VigiBase have been internationally acknowledged as leaders in the field. However, patient safety is no simple matter, and we have to be sure that our methods take full account of complexity. This latest development by the research team is another important step towards our goal of *never missing a signal*."

Kristina Juhlin, Kristina Star, G. Niklas Norén are from UMC's Research Team; Xiaofei Ye was a visiting PhD student, Dept of Health Statistics, Second Military Medical University, Shanghai.

Full details of the project and the method can be found in reference 5 below:

1. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, et al. A Bayesian neural network method for adverse drug reaction signal generation. *Eur J Clin Pharmacol.* 1998;54(4):315–21.
2. Norén GN, Orre R, Bate A, Edwards IR. Duplicate detection in adverse drug reaction surveillance. *Data Mining and Knowledge Discovery.* 2007;14(3):305–28.
3. Strandell J, Caster O, Hopstadius J, Edwards IR, Norén GN. The development and evaluation of triage algorithms for early discovery of adverse drug interactions. *Drug Safety* 2013;36(5):371–88. Epub 2013/05/04.
4. Hopstadius J, Norén GN. Robust discovery of local patterns: Subsets and stratification in adverse drug reaction surveillance. *Proceedings of the 2nd ACM SIGHIT International Health Informatics Symposium.* 2012:265–74.
5. Juhlin K, Ye X, Star K, Norén GN. Outlier removal to uncover patterns in adverse drug reaction surveillance – a simple unmasking strategy. *Pharmacoepidemiol Drug Saf.* 2013.

Advances in e-Learning

Anders Viklund and Ulrika Rydberg

Do you know how to do a Sauce Hollandaise? Some people use cookery books, but isn't it easier to watch a step-by-step video clip? UMC Education & Training proudly presents two new video based e-Learning courses on the tools **VigiFlow®** and **VigiLyze™**.

VigiLyze

VigiLyze is a search and analysis tool that provides access to the WHO Global ICSR database, VigiBase®. The VigiLyze e-Learning course consists of several video clips that guide you through the tool.

The aim is to provide 'get-it-at-once' information on how to operate the tool as a complement to the more conventional on-

line help section in VigiLyze. The course videos include the screen, cursor movements and narrator's voice, recorded by UMC staff.

VigiFlow

We now offer two courses on VigiFlow – 'the complete ICSR management system'. The new course is called 'VigiFlow introductory videos' and consists of videos of the VigiFlow interface as specific tasks are performed. This starter course is primarily for new users of VigiFlow, but more proficient users can also, for instance, get fresh insights into how most efficiently to find and add a reaction term. These videos do not have sound, instead written instructions are given in the course interface. The existing VigiFlow course is offered in parallel and gives more in-depth information and interactive exercises.

More courses?

The new courses are part of an effort to provide more web-training on our tools. We hope to be able to offer more and better training in the future and invite you to suggest improvements that would be helpful to you. All suggestions – new topics within these courses, new courses, video or interactive, technical troubles that need resolving, etc – are welcome!

Course information

Who has access?

Anyone with a VigiFlow or VigiLyze account

What is the cost?

Free of charge

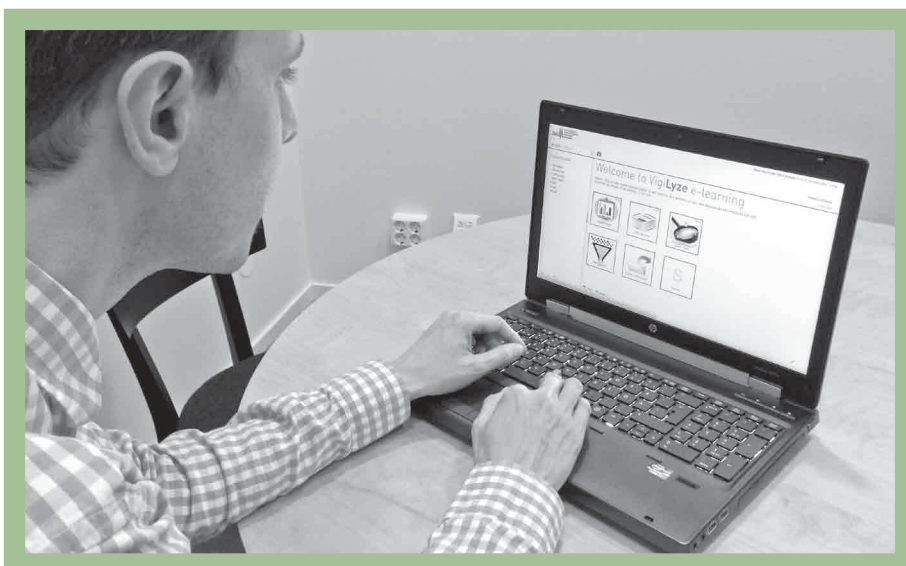
Is there a time limit?

Each access period is 90 days. It is renewable.

How do I register?

Contact pvtraining@who-umc.org

VigiLyze has already made a big impression on national centre staff who have used it so far. Many of those attending the Rome WHO Programme meeting were complimentary on its possibilities. We were also delighted to receive an unsolicited message from one European centre: "I feel a need to present to you my standing ovations for VigiLyze: I now use it all the time for quick analyses and check-ups in our part of the EU signal detection work. Brilliant development!"



Learning at your computer

Erice Declaration translations

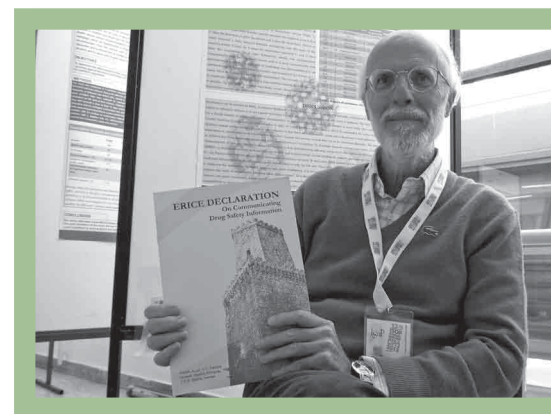
Geoffrey Bowring

The vision of the Erice Declaration (1997) was to influence thinking and practice in the area of drug safety communication: a vision of openness, transparency and independence, the belief that drug safety communication was to serve the health of the public.

After its publication, the Erice Declaration was widely cited in the literature, and translated into a number of languages. Professor Giampaolo Velo of the Clinical Pharmacology Unit in Verona was the principal instigator of the conference and subsequent Erice meetings.

This booklet gathers together both existing translations along with some newly-commissioned for its publication. All official WHO languages are included. After the English original, there are French, Spanish, Chinese, Arabic, Russian, Portuguese, Japanese, Italian and Swedish translations. This reprint is a reminder of the continuing importance of striving towards a world in which effective drug safety communication and patient safety should be given the highest priority.

The booklet is available by contacting the UMC. Separate language versions will be made available in the near future.



Giampaolo Velo with the new Erice Declaration booklet.

DIA in Boston

Helena Sköld

The 49th annual meeting of the DIA (Drug Information Association) 2013 took place in the very nice city of Boston, Massachusetts in USA. The grand exhibition and conference venue was appropriate for this meeting – great in both attendee numbers and in content.

Twenty tracks

The keynote speaker Daniel Kraft, a Stanford and Harvard trained physician-scientist, inventor, entrepreneur and innovator (and pilot (!)), made a good job setting the scene for the meeting with an exhilarating key-note speech on the subject of eMedicine and eHealth.

The meeting had over 20 different tracks and it is impossible to give any kind of summary of such a huge meeting, so let's settle for that there were a lot of interesting

subjects and most speakers were very experienced in their fields; all-in-all it was a good place to be, both for networking and for competence development.



UMC staff Mikael Nilsson, Jessica Avasol and Madeleine Krieg at the UMC stand in Boston

Uppsala reports

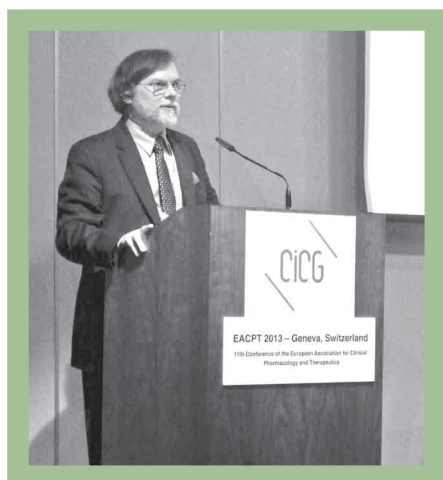
The UMC was represented in the programme by Niklas Norén (Chief Science Officer) who chaired and/or presented in three sessions of

Track 14 – Clinical Safety and Pharmacovigilance: 'Electronic Health Records (EHRs) in Signal Detection and Evaluation', 'EU Update: PROTECT and EnCePP', and last but not least 'Molecular Predictors of Drug-induced Harm: From Clinical Development to Post-marketing Surveillance'. All sessions were well attended despite some heavy competition from other tracks.

UMC also had a busy booth at the DIA exhibition, enabling us to connect (in a non-electronic way) to both current and future customers and partners.

Pharmacovigilance for European Pharmacologists

Sten Olsson



Andrzej Czarnecki speaking in Geneva

The 11th congress of the European Association of Clinical Pharmacology (EACPT) was held in Geneva, Switzerland from 28–31 August, 2013. About 550 professionals from all over Europe attended. Three sessions sponsored by WHO were devoted to medicine safety and pharmacovigilance and were chaired by Lembit Rägo and Shanthi Pal:

Current trends in global pharmacovigilance

- Andrzej Czarnecki spoke on 'Safety information today and how can we improve patient safety tomorrow'
- Adrian Llerena presented population pharmacokinetics and its implications for pharmacovigilance.

Pharmacovigilance networks

- Henry Fitt gave a talk on 'ENCEPP: Strengthening methodology, transparency and independence'
- Shanthi Pal introduced the WHO Programme for International Drug Monitoring
- Gianluca Trifirò presented 'What is the additional value of electronic medical records for drug safety signal detection? The experience of the EU-ADR project.'

Drug safety in emerging countries

- Ambrose Isah talked about drug safety in emerging countries – a perspective from Nigeria
- Mariano Madurga Sanz gave a Latin-American pharmacovigilance update
- Sten Olsson gave an overview of pharmacovigilance in resource-limited settings.

It is most encouraging that clinical pharmacologists in Europe are paying sufficient attention to pharmacovigilance and medicine safety to devote three specific sessions to these topics, and that they liaise with WHO and its International Drug Monitoring Programme to assist in engaging the speakers.

ISPE hears the patient's voice

Kristina Juhlin

The annual ICPE (International Conference on Pharmacoepidemiology) in Montreal, Canada from 26-28 August was well organized and full of interesting sessions. Generally six sessions ran in parallel, one of which was always a methods oriented session. Sessions were well attended with good questions and discussion.

software for automatically detecting information on ADRs from social media.

Harmonizing methods and data across databases

Xiaofeng Zhou of Pfizer described their experience of adapting the The Health Improvement Network (THIN) database to

Unlocking the secrets of free text

This section focused on Natural Language Processing (NLP) and why it is important. Sascha Dublin introduced the concept of NLP and described how structured terminologies often cannot capture all information on a case and how coded information may well be inaccurate. Imre Solti then continued by giving a general introduction on how to work with NLP.

UMC presentations

I presented posters on unmasking and PROTECT 3.12 (duplicate detection); on day two the UMC poster ((PROTECT 3.10 – comparison of electronic health records to epidemiology studies), presented by Alex Asimwe attracted a lot of interest with people asking questions and taking abstracts.

Marie Lindquist presented a well-needed perspective on the importance of not over-fitting new methods to already known signals by using a reference set of well-known events, during the 'Impact of the Choice of Reference Set on Performance Testing of Signal Detection Methods' symposia. My presentation on the work done within PROTECT 3.01 (A comparative evaluation of disproportionality measures) was within the 'sounding all the sources' session and received positive feedback.



Poster browsing in Montreal...

Noteworthy presentations

Ryan Kaplan, a high school principal, cyclist and MS patient talked about living with MS since the age of 15 and his choice of switching to tysabri despite the risk of PML (progressive multifocal leukoencephalitis). Company (Gary Bloomgren) and regulatory (Stella Blackburn, EMA) representatives complemented his presentation with facts about the risks of contracting PML for different groups. Kaplan argued for the patient's right to be part of the decision on which medication to take, and several speakers during this session pointed out that what is an important benefit or risk for one patient might not at all be important for another.

the OMOP common data model (CDM). Adapting a database to a CDM requires an in-depth understanding of that database, including clinical aspects, and is a major commitment that requires both medical and



... and refreshment time

The patient's voice

Ethan Basch compared clinicians' and patients' reports of the patient's experience. According to Basch clinicians tend to miss or downgrade symptoms; reports from patients generally correlate better with functional status. There is no evidence that patients are reporting non-relevant symptoms and patients are generally better at detecting adverse symptoms than clinicians. He recommended using patient data for identifying ADRs, for comparing tolerability of products and for deciding the dosage of a drug. Nabarun Dasgupta spoke on FDA's use of mobile apps and social media to monitor and identify ADRs. He demonstrated

technical knowledge. Among the challenges, she mentioned the risk of information loss due to the different database structures, mapping different terminologies and ensuring completeness of data after conversion. She also pointed out that organizations might interpret the CDM in different ways. Patrick Ryan described the development of the OMOP CMD and how additional areas of usage are added as the CDM grows.

The social side

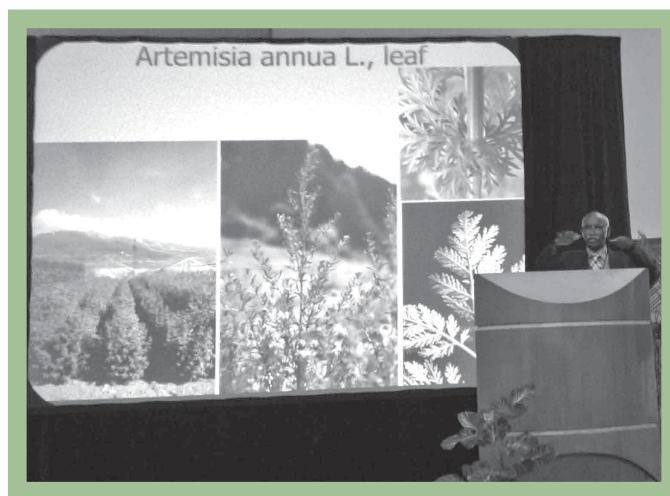
ISPE is making big efforts to make new members and young professionals feel at home and welcome including a students/young professionals night out and new members were encouraged to take part of the meetings of the special interest groups as well as round table discussions during lunch breaks. Another happy reunion for us was Xiaofei from Shanghai, China who spent six months in the Research department at the UMC in 2011.

United moves in Mexico

Elki Sollenbring

The Mexican National Pharmacovigilance Centre, in collaboration with the Mexican Pharmacovigilance Association, recently organized the VII National Pharmacovigilance Congress. Entitled 'United by a proactive and effective pharmacovigilance, for the safety of patients', it took place in the west coast resort of Ixtapa, in Zihuatanejo, from 4-6 September 2013.

The congress was attended by 29 State Centres of Pharmacovigilance (part of the Mexican pharmacovigilance system) and by 14 Institutional Pharmacovigilance Centres, in addition to



Mohamed Farah speaking at the Mexican national congress

284 national congressmen, 21 speakers, and two international speakers. There were seven plenary conferences, two roundtables, two simultaneous workshops, one general workshop and 14 poster presentations.

During this congress Dr Mohamed H. Farah, Senior Specialist, Traditional Medicine at the Uppsala Monitoring Centre, spoke about the importance of watching for the effects of traditional medicines and their possible interactions with allopathic medicines, to ensure a safe use of these as part of the pharmacovigilance activities.

Pharmacovigilance Fellowship

Haggar Hilda Ampadu

From mid-June to mid-July the WHO Collaborating Centre for Advocacy and Training in Pharmacovigilance organized a four-week Pharmacovigilance Fellowship in collaboration with Santé-Afrique Ltd and Sanofi. In all, five participants from two African countries and one European country were represented. These were from Sierra Leone, South Sudan and the United Kingdom.

Aims of the four weeks

The training was divided into:

- Week 1 – Theory and practice of pharmacovigilance
- Week 2 – Practical hands-on training
- Week 3 – Field work
- Week 4 – Wrap-up and Evaluation.

The course objectives were:

- To provide training in the theory in pharmacovigilance
- To provide hands-on experience in pharmacovigilance tools and associated software
- To provide field visits and appreciate real life practice of pharmacovigilance in hospitals, regulatory and real life settings.

The first week saw the participants through the theory and practical aspects of pharmacovigilance which involved face-to-face sessions with facilitators and experts in the field. These included experts from the Uppsala Monitoring Centre-Africa and the Ghana Food and Drugs Authority (FDA).

Recording of ICSRs; VigiFlow and VigiBase, Searching and Analyzing ICSRs from the WHO database, Communication and Crisis Management. The week ended with a trip to the Kwame Nkrumah Mausoleum during the afternoon session.

In the field

During the third week participants went out to institutions in Ghana involved in pharmacovigilance; the Dodowa Research Centre, the Ghana Food and Drugs Authority, the Ghana Police Hospital. During the final week participants were trained in soft skills relevant to their work as pharmacovigilance experts. This included introduction to CemFlow, a data management tool for collection and analysis of data from Cohort Event Monitoring (CEM) programmes, funding, a hands-on session on the use of survey tools such as google drive, and other relevant topics.



Participants, facilitators and staff during the Fellowship weeks

Hands on

In the second week, there were a number of hands-on sessions, as well as theoretical, along with open discussion forums. The hands-on sessions: Management of Individual Case Safety Reports (ICSRs),

The participants performed brilliantly when they presented a selected topic to their colleagues and the consultants. The last day of the week saw presentations of certificates and a final course evaluation.

Toolkit expands further

Alex Dodoo

The Pharmacovigilance Toolkit is now well established, but is not sitting still. Upgrades are happening all the time. The Malaria PV toolkit is now online. We do of course incorporate the views and suggestions from users where possible during the upgrades.

Toolkit is maintained by UMC-A and by the WHO Collaborating Centre in Accra. New content is written and developed by experts such as Ralph Edwards (causality assessment) and Bruce Hugman (communications), which is also checked by UMC experts and at WHO. The new Toolkit contents are endorsed by the WHO Advisory Committee on the Safety of Medicinal Products before being uploaded by UMC-A.

One recent addition has been information and links related to drug utilization and ATC/DDD.

The aim of translating the Toolkit into the various WHO official languages is still in view: some pages are now accessible in Spanish.

The development of Vaccine Pharmacovigilance Toolkits is in progress. This will bring to one space, all WHO-approved or WHO-recognized methods, procedures and guidelines for vaccine pharmacovigilance (<http://vaccinepvtoolkit.org/>)

For all information, please e-mail info@who-pvafrika.org.



Pharmacoepidemiology textbook

The Textbook of Pharmacoepidemiology by Brian L. Strom, Stephen E. Kimmel and Sean Hennessy has had its 2nd edition published online by John Wiley & Sons Ltd. It includes a chapter on 'Postmarketing Spontaneous Pharmacovigilance Reporting Systems' by Gerald Dal Pan (Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research, US Food and Drug Administration), Marie Lindquist (Uppsala Monitoring Centre), and Kate Gelperin (US FDA).

The publishers aim the book at senior undergraduates, graduate students, post-doctoral fellows in public health, pharmacy and medicine, and "for everyone learning and working in pharmacoepidemiology". It covers pharmacoepidemiology and "the data sources, methods and applications used in clinical research, the pharmaceutical industry and regulatory agencies". New features include case studies, key points and further reading suggestions, flagged throughout.

Print ISBN: 9781118344866, Online ISBN: 9781118344828

UMC course 2014

The UMC's 16th international pharmacovigilance training course will take place in Uppsala, Sweden from 7-21 May 2014.

The aim of the course is primarily to support the development of programmes for spontaneous adverse reaction reporting and to give an introduction to other methodologies. The target audience is health care professionals, e.g. physicians, pharmacists, nurses, recently engaged or soon to become engaged in the practical operation of pharmacovigilance programmes in a hospital, community, regulatory, university or industry setting.

[More from the UMC website.](#)

WHO Programme interviews

At the World Research and Innovation Congress in Brussels in June 2013, Shanthi Pal and Sten Olsson participated to present some results of the Monitoring Medicines project. During one of the breaks they were interviewed by a journalist from the open source journal *International Innovation*. The resulting article is available on page 110 – 111 via this link: <http://www.research-europe.com/magazine/HEALTHCARE2/EX14/index.html>

A round-up of recent UMC papers

The Impact of Duration of Treatment on Reported Time-to-Onset in Spontaneous Reporting Systems for Pharmacovigilance.

Karimi G, Star K, Norén GN, Hägg S. *PLoS ONE*, 2013, 8(7): e68938. doi:10.1371/journal.pone.0068938.

Time-to-onset is the definition of how long it took for an adverse reaction to occur after treatment started. The research team at UMC investigated reported in relation to expected time-to-onset, and the variability as between short- and long-term treatment. They found that adverse drug reactions reported for short-term treatments are generally reported with shorter latency than that expected by the nature of the mechanism of the event; events with long time-to-onsets are not reported and thus not captured for the short drug treatments.



For drug safety data analysis, the findings mean that the reported time-to-onset is affected by the duration for which the drug is in use and will be shorter than expected for long latency events.

Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery.

Norén GN, Hopstadius J, Bate A. *Statistical Methods in Medical Research*, 2013, 22(1):57-69

This recent methodological publication differs from many others in that it does not propose increased sophistication, but rather the simplification of an existing method. Specifically, it offers a simplified way to compute the Information Component (IC),



which has been the basis for data mining in the WHO Programme for International Drug Monitoring since the late 1990s. It is the measure of association in routine use throughout the WHO Programme's analytical suite, including our methods to screen for adverse drug interactions and temporal associations in longitudinal electronic health records.

The Development and Evaluation of Triage Algorithms for Early Discovery of Adverse Drug Interactions.

Strandell J, Caster O, Hopstadius J, Edwards IR, Norén GN. *Drug Safety*, 2013, 36(5):371-388

The research team at UMC has recently developed a novel and productive approach to detecting possible harm caused to patients by interacting drugs and other substances from information in the database. In the UMC's new system, individual patient case information and pharmacological plausibility have been added to the statistical association analysis, greatly strengthening the power of the search process to capture possible interactions.

This triage method has shown a marked increase in performance and accuracy over previous methods and should lead to the identification of previously unknown risks.

At this early stage, a number of suspected cases of new interactions generated by the method are being reviewed by clinical experts, but the method has been shown to reliably identify previously unrecognised cases of known interactions, a major step forward in itself.

Key Elements in Adverse Drug Interaction Safety Signals – An Assessment of Individual Case Safety Reports.

Strandell J, Norén GN, Hägg S. *Drug Safety*, 2013, 36(1):63-70

Whereas it is generally well-understood what constitutes a strong individual case report in the assessment of adverse reactions to single drugs, much less is known about the assessment of adverse drug interactions. In this study, UMC and Linköping University researchers explored the nature of individual reports that had supported historical signals of adverse drug interactions. The study found that key elements in adverse drug interaction safety signals include plausible time courses and resolution of the adverse reaction upon withdrawal of the drug suspected to have induced the interaction. A plausible time course for an adverse drug interaction may be that the adverse event occurs soon after exposure to a drug without known risk of the adverse event, in a patient already on stable treatment with a drug that is known to carry this risk.



Logistic Regression in Signal Detection: Another Piece Added to the Puzzle

Caster O, Norén GN, Madigan D, Bate A. *Clinical Pharmacology and Therapeutics*, 2013, doi:10.1038/cpt.2013

This letter to the editors of *Clinical Pharmacology and Therapeutics* comments on and complements a recent publication in that journal on the use of logistic regression as an

alternative to standard disproportionality analysis in pharmacovigilance signal detection. The letter specifically clarifies the extent and the nature of UMC's previous contributions to this research area, including three prospective safety signals that have been published in the *WHO Pharmaceuticals Newsletter* during 2012 and 2013.



Challenges of safe medication practice in paediatric care – a nursing perspective.

Star K, Nordin K, Poder U, Edwards IR. *Acta Paediatrica*, 2013, 102(5):532-538

Twenty registered nurses from four paediatric wards at two hospitals in Sweden were interviewed in focus groups, followed by a content analysis.

Nurses found paediatric medication technically complex and supported each other in resolving issues such as complex calculations, unanticipated problems (concerning non-paediatric dosage forms), unclear prescription or product label instructions, emergency situations. The nurses felt that achieving safety whilst medicating children was challenging and psychologically taxing, partly because of the communication challenges children present, and when parents are intermediaries.

Nurses had limited success in changing medication practices even when repeated requests to management for improvements had been made. In spite of their critical role in administering medicines correctly and safely the focus was primarily on the needs of doctors and pharmacists. In particular the informatics systems that were intended to improve the supply chain to the patient had not incorporated the needs of nurses.



A nationwide multidisciplinary collaboration between hospitals was recommended to increase safe medication practices in paediatric care.

Verona Masters

Anna Coggiola Pittoni



Director of the Master's course, Professor Roberto Leone, with his collaborators

Recent years have witnessed considerable evolution in pharmacovigilance practice leading to greater need for people trained in this field. In Italy there are four academic related courses. At the University of Verona, since 2011, the Pharmacology Unit has been providing a 'Master Universitario' in Pharmacovigilance and Regulatory Affairs. Theoretical knowledge, practical skills and competencies acquired by the student during the Master are mainly those required of a head of pharmacovigilance (both public and private), but they are also appropriate for the office of regulatory affairs in a pharmaceutical company. Preparing for the

fourth intake, our course lasts one year, and is aimed both at students holding a Bachelor's degree and a Master's in Pharmaceutical, Biological, Medical and Chemical Sciences.

Teaching methods are various: traditional face-to-face lectures, practical exercises (e.g. in epidemiology and PSUR), and the final modules in risk communication are provided through an interactive e-learning platform.

Broad faculty

Lecturers come from the public sector, such as universities, Italian Medicines Agency,

Uppsala Monitoring Centre (UMC), National Institute of Health, Regional Centres of Pharmacovigilance, and the private sector, such as pharmaceutical companies. Both sectors offer internships during which the student has the opportunity to improve his or her practical skills and to strike up good relationships with experts in drug safety. For instance, two students have spent six months in the UMC, working in signal detection on spontaneous reporting in VigiBase.

So far, in three years, 55 students have attended the course. Some of them have strengthened their own position within the companies they worked for, others used it to completely change their working area, and others (younger graduates), have for the first time broken into the world of work.

More information about the Master can be found at the website <http://www.univr.it/master>.

European collaboration

The University of Verona also collaborates in a consortium of seven universities, the European and French medicines agencies and 15 pharmaceutical companies, who have embraced the 'European Programme in Pharmacovigilance and Pharmacoepidemiology' (Eu2P). Eu2P offers Master, PhD and Certificates, all delivered through an e-learning platform and web-based examinations developed specifically for this project. More information can be found at: <http://www.eu2p.org>.

New faces

Jonas Ahlkvist was born and raised in Uppsala and studied Computer Science at the University of Uppsala. He lives with his wife and three boys in the area known as Gamla Uppsala ('Old Uppsala' where Viking burial mounds are found). His position is Section Manager for PDQ IT Development, ensuring that the UMC efficiently delivers its products and services to our customers.

"Before joining UMC I have been working as a consultant, assisting organizations to develop systems that support users as well as being achievable and maintainable. Prior to that I worked with product development, from software developer, through system architect, project manager and finally product manager. One of my tasks involved changing the business model to provide some of the products as open source which was a bit of a challenge."

"My family and I are quite into sports: I am training and coaching the floorball team

my youngest son plays in. In my spare time I like exercising and cooking, fortunately a good combination. I also own a pinball game from 1977, Williams Big Deal, which I try to keep in good shape. You can see a pinball machine like it in the movie 'Get Shorty' or just join me for a game."

Pekka Häkkinen was born and grew up in Upplands Väsby, a suburb 20 km north of

Stockholm. As the new Section Manager - Product Management, his main responsibilities include managing UMC's team of product managers in collecting customer needs, creating product plans, creation of product portfolio and marketing plans.

His previous work includes senior positions at Maquet Critical Care and 3M, following his MScBA, Marketing, Finance, Mathematics at Stockholm University.



Jonas and Pekka

"I enjoy reading history about mythologies/wars/people, and my never-ending curiosity leads me to test/practice things without the ambition to master them, so I have a broad hobbies portfolio: fishing, climbing, playing guitar, building on the house, building model planes, solving riddles, gym visits, etc. In short, I make sure that the head has some 'fun' when it has leisure time."

*

We recently bid farewell to **Daniel von Sydow**, who had worked in products and services at the UMC since 1999.

Paediatric pharmacist From Kathmandu

In August we had a pleasant visit from **Paulo Caceres Guido**. He is a pharmacist at a paediatric hospital in Buenos Aires, Argentina. Having attended a pharmaco-metrics course at Uppsala university he took the opportunity to come and visit us. He was very interested to learn about our work, especially the signal detection and research areas.



Elki Sollenbring, Paulo Caceres Guido, Cecilia Biriell

Hanna Pedersen

In September the UMC had a visit from **Mr Eurek Ranjit**. He is a pharmacist/pharmacologist working as a Lecturer at Kathmandu Medical College Teaching Hospital in Nepal. Mr Ranjit spent three weeks in Linköping, Sweden to participate in a faculty exchange programme between Kathmandu Medical College and Linköping University. At Linköping he gave a number of presentations to the Swedish students, for example about pharmacy in Nepal.

During his stay in Sweden, he took the opportunity to visit UMC for half a day, learning more about the WHO Programme for International Drug Monitoring, the work of the Uppsala Monitoring Centre, as well as discussing the current status of the pharmacovigilance system in Nepal.



Eurek Ranjit with Hanna Pedersen

DATES	TITLE	PLACE	ORGANISER/CONTACT
6-7 November 2013	Signal Management in Pharmacovigilance	Paris, France	DIA Europe Tel.: +41 61 225 51 51 Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org www.diahome.org/en-GB/Meetings-and-Training.aspx
13-14 November 2013	Pharmacovigilance in Products Subject to Licensing Agreements	London, UK	Drug Safety Research Unit Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org www.dsru.org/trainingcourses
13-14 November 2013	X Encuentro de Farmacovigilancia de las Américas	Barranquilla, Colombia	Health Ministry/INVIMA, National University of Colombia, PAHO
18-19 November 2013	Large Databases for Safety Monitoring	Washington DC, USA	DIA www.diahome.org
22-24 November 2013	XIII Annual Conference of Society of Pharmacovigilance of India 'India: Towards achieving global standards of Pharmacovigilance'	Karamsad, Gujarat, India	E-mail : sopicon2013@charutarhealth.org barnaganguly@rediffmail.com
27-28 November 2013	Pharmacovigilance Planning and Risk Management	Fareham, UK	Drug Safety Research Unit (as above)
28-29 November 2013	Latest Developments in Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 730008 E-mail: registrations@management-forum.co.uk www.management-forum.co.uk
12-13 December 2013	First African Congress of Pharmacovigilance – Pharmacovigilance in Africa, situation and perspectives	Rabat, Morocco	African Society of Pharmacovigilance E-mail : smpvmaroc@gmail.com www.smpv.ma
16-18 December 2013	Pharmacovigilance	London, UK	Management Forum Ltd (as above)
Tutorials: 12 January 2014; Conference: 13-15 January 2014	Annual DIA Pharmacovigilance and Risk Management Strategies	Washington DC, USA	DIA Clinical Safety and Pharmacovigilance Community Tel.: +1 215 293 5810 Fax: +1 215 442 6199 E-mail: Ellen.Diegel@diahome.org www.diahome.org/
3-7 February 2014	International Meyler Course in Pharmacovigilance 2014	Groningen, The Netherlands	University of Groningen. By invitation; CVs and explanation of why you should be invited to be sent to Eugene van Puijenbroek (e.vanpuijenbroek@lareb.nl)
3-4 April 2014	Proactive Pharmacovigilance and Risk Management in the Era of Personalised Medicine	Zagreb, Croatia	International Society of Pharmacovigilance E-mail: administration@isoponline.org www.isoponline.org
4-7 April 2014	ISPE Mid-Year Meeting	Rotterdam, The Netherlands	ISPE E-mail: ISPE@paimgmt.com www.pharmacoepi.org/meetings
5-9 May 2014	Data Management for Clinical and Regulatory Affairs	Accra, Ghana	UMC-A Tel: +233 302268746 E-mail: training@who-pvafrica.org www.who-pvafrica.org
22-23 May 2014	UMC Research Conference 2014 – Risk: What risk? Whose risk?	Uppsala, Sweden	Uppsala Monitoring Centre www.who-umc.org
16-27 June 2014	8ème Cours Francophone de Pharmacovigilance	Rabat, Morocco	Centre Anti Poison et de Pharmacovigilance du Maroc Tel: +212 5 37 77 71 69 E-mail : louammi@gmail.com www.capm.ma
24-25 July 2014	Introduction to Pharmacovigilance	Accra, Ghana	UMC-A (as above)
24-27 October 2014	30 th Anniversary ICPE	Taipei, Taiwan	ISPE (as above)



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 VigilYZe™ 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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A list of UMC staff may be found via -
About UMC > UMC staff - on our website.

Internet: www.who-umc.org

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