



MUR49

5 million reports

Behind the computer screen

CIOMS at 60

WHO Programme news

CEM in HIV/AIDS





Marie Lindquist
Director
the Uppsala Monitoring
Centre

Some time ago I had an interesting email in my inbox: I was asked if I know of any examples of reports of adverse events which later were shown not to be correct or where the incidence is no greater than that observed for the disease itself.

This made me think about the concept of 'true' and 'false' signals, and the associated challenges involved in signal detection.

Signal detection is about identifying risks. If an attribution of an adverse effect of a drug is correct, and the consequent actions taken are appropriate, patient harm can be avoided. As far as possible we must try to ascertain that there is sufficient information supporting a signal hypothesis when it is first raised. At this stage we do not always have proof of causality on the individual level; even less likely evidence of an increased incidence in the population, attributable to the suspected drug.

What evidence do we need before we consider a signal 'true'? To what extent must the Bradford Hill criteria have to be met, keeping in mind his advice that "None of these nine viewpoints can bring indisputable evidence for or against a cause and effect hypothesis What they can do, with greater or less strength, is to help answer the fundamental question – is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"¹. Can evidence from case reports alone ever be enough? If not, does one affirmative epidemiological study constitute proof?

Another consideration is the timing of signalling. Early signals may not be verifiable for some time. Epidemiological protocols or experimental work need to be conceived, implemented and analysed before a result is forthcoming; this may take years.

We should definitely be concerned about raising false alarms, which could be the result of going out with a signal without good supporting evidence. In the most drastic case, a signal can lead to the withdrawal of a drug which for many patients could mean that they have to use less effective alternatives, or alternatives with different adverse reaction profiles – which could be just as bad, or worse, for them. Reported adverse events, when printed in the product labelling, could have similar effects if they deter doctors from prescribing a product when it would have been the best alternative. Also, the companies producing the implicated products may suffer both economic losses and negative publicity that may have a serious negative impact on them.

But does the absence of positive proof mean that a signal is 'false'?

If affirmative evidence from epidemiological studies is taken as confirmation that a signal is 'true', does the absence of such evidence invalidate a signal based on case reports, even if the diagnoses were correct and the individual causality assessments support the hypothesis?

What about a situation where the background incidence of a disease is relatively high and the extra cases caused by drug X are too few to produce a significant increase in overall incidence in an epidemiological study? This does not mean that X could not have caused the reaction: it may be that the power of the study is too low.

My conclusion is that the risk of producing 'false' signals must not stop us from trying, even if we cannot say for sure that all signals we find are 'true'. We do have to make clear in our communications, though, that early signals are tentative and not proof – a signal is always a start, and never the end.

¹ <http://www.southalabama.edu/coe/bset/johnson/bonus/Ch11/Causality%20criteria.pdf>
Accessed March 23, 2010

A handwritten signature in black ink that reads "Marie Lindquist".



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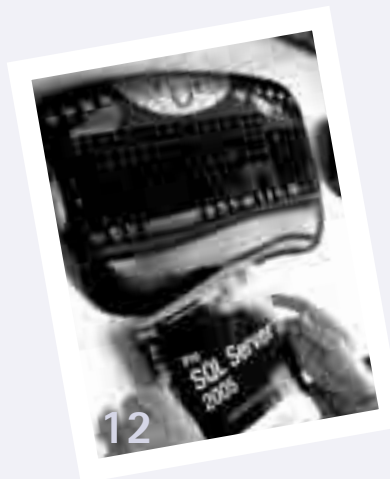
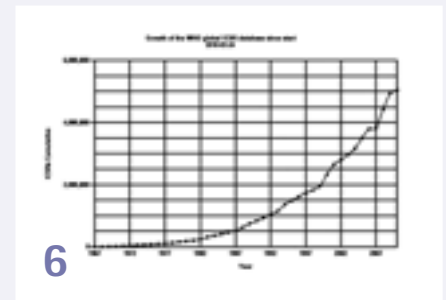


Accra

Accra prepares to welcome National Centres Meeting to the first meeting of the WHO Programme in sub-Saharan Africa later in 2010.

5 million reports

The WHO global database reaches 5 million reports: we present the trends in ADR data held at the UMC.



PDQ

Meet the backroom staff of the UMC's Production, Development and Quality department.

The UMC out and about

News from pharmacovigilance centres around the world.



New full member of the WHO Programme

Zambia



Oscar Simooya

We have received a notification that forty reports from the national centre in Zambia have been entered in VigiBase, using VigiFlow. Zambia has been an Associate Member since 2003 and has now become the 97th full member of the WHO Programme for International Drug Monitoring.

The national centre in Zambia is currently outsourced from the regulatory authority in Lusaka to University of Kitwe in the northern part of the country. Oscar Simooya is the contact at the pharmacovigilance centre and we hope to print an introductory article on the national drug safety plans for the country in the next issue.

New associates

Four countries have applied to become members of the Programme during the last quarter:

Guinea – a focal point for pharmacovigilance has been designated within the Direction Nationale de la Pharmacie et du Laboratoire in the Ministry of Health and Hygiene in Conakry.

Mali – A Reference Centre for Pharmacovigilance has been created within Koulouba the 'Centre National d'Appui à la lutte contre la Maladie' (CNAM); a national pharmacovigilance committee is also to be set up.

Azerbaijan – the Analytical Expertise Center for Medicines in Baku in the Ministry of Health has applied to become a member of the WHO Programme.

Bosnia and Herzegovina – a pharmacovigilance unit has been established at the Agency for Medicinal Products and Medical Devices in the city of Banja Luka.

Fast progress for Peru

Using the VigiFlow case management system the Peruvian national pharmacovigilance centre 'Centro Nacional de Farmacovigilancia' have sent a large number of ICSRs to the UMC over the last few months, so that almost all reports (over 8,000) collected in Peru since the inauguration of their system in 1999 are now available in the global database, VigiBase. We commend this major effort by colleagues at the Peru national centre, who have been using the Spanish version of the software. The participation of Kelly E Serrano Mestanza (Pharmacist at the national centre) in the 2009 Uppsala training course has been a helpful stimulus to this improvement.



Kelly Serrano

Australian changes

After 39 years, since its inception in 1970, ADRAC (Adverse Drug Reaction Advisory Committee) has been dissolved; in future the Australian TGA (Therapeutic Goods Administration) will be served by a new committee, the Advisory Committee on the Safety of Medicines (ACSOM), which will have broader terms of reference than the previous

one, including advising the TGA on the quality and appropriateness of risk management plans.

The ADRAC has been the cornerstone of post-marketing safety monitoring in Australia and was remarkably effective – highlighting emerging problems with medicines and contributing to world-wide drug safety.

The end of ADRAC also marks a new format for the Australian Adverse Drug Reactions Bulletin, which is being replaced by a new medicines safety publication alongside *Australian Prescriber* (available from the www.australianprescriber.com website).

New start for Viet Nam

The Ministry of Health in Viet Nam has informed the UMC of a re-organisation of drug safety monitoring in their country. Contrary to a popular trend in many other countries the national pharmacovigilance centre has been moved from the Drug Administration of Vietnam to a new centre at the Hanoi University of Pharmacy (HUP) which will oversee the activities of the National Drug Information and Adverse Drug Reaction Monitoring Centre, inaugurated on 9 June 2009.

The new Centre is responsible for supporting the Ministry of Health to build up and provide a sound drug information database and is an independent, statutory unit, and the focal point of contacts with the WHO Programme. The Director of the Centre is Professor Nguyen Dang Hoa.

The statutes forming the Centre specifically include responsibilities for training of under- and post-graduates and other health workers in pharmacovigilance, for research, for international co-operation, as well as for communication with regional and local drug information and ADR centres.

We look forward to further improved collaboration with colleagues in Viet Nam.

Direct patient reporting now in Norway



The Norwegian Medicines Agency launched a new mechanism for reporting of suspected adverse reactions directly from patients on 1 March 2010. Reporting can only be done through the website of the agency. You have to sign up with your personal details but can report suspected reactions happening to a close family member. The reporting site contains general information about ADRs and what to do if you think you are affected by one. The new route of reporting is supported by a promotional poster.

WHO Programme support in Geneva

Since the retirement of Dr Mary Couper, Dr Shanthi Pal has been undertaking the role of Acting Programme Manager for the Safety of Medicines and Pharmacovigilance Programme at WHO Headquarters in Geneva. The staffing at the QSM Department (Quality, safety and efficacy of medicines) in Geneva

currently consists of Dr Shanthi Pal, Ms Mitsuko Imai (Technical Officer, seconded from the Japanese government), and secretaries Ms Maria Cuadrillero and Ms Ana Garcia.

During April to June, Cecilia Biriell, a Senior Specialist at the UMC is undertaking a secondment to the QSM Department to assist with several projects, including the WHO list of restricted drugs.



Mitsuko, Shanthi (front); Ana and Maria (back) - the team in Geneva



Kees van Grootheest speaks to assembled health professionals in Paramaribo

Suriname guide launch

Jerry Labadie (UMC) and Kees van Grootheest (Lareb, the Netherlands) were invited speakers at a Ministry of Health symposium on drug safety on February 6 in Paramaribo, Suriname. During this symposium, Naomi Jessurun and Pearl Tjin A Kwie of the Suriname National Pharmacovigilance Centre proudly launched the 22-page national guideline on how to handle adverse drug events.

The symposium was attended by over 70 health care professionals and the guideline was well received. During the visit the opportunity was taken for the visitors and national public health officials to compare notes about safety monitoring during national immunization campaigns with pandemic influenza vaccine – Suriname's campaign was about to start on February 10.

VigiBase – ICSR reporting from member countries

Sara-Lisa Fors and Helena Wilmar, Reporting, Analysis & Country Support

More reports in WHO global database

The UMC is pleased to report that - thanks to the continuing submission of Individual Case Safety Reports (ICSRs) from member countries of the WHO Programme for International Drug Monitoring - the number of ICSRs in VigiBase™ (the WHO global ICSR database) passed the milestone of 5 million in late February, making VigiBase the largest ICSR database in the world.

The number of ICSRs increases quickly with the fast growth of the WHO Programme (96 member countries today). Compared with the 25 years it took to receive the first million reports in 1992 (at which time the WHO Programme had 36 members), it took only 18 months to receive the last one million ICSRs.

Reporting rates and Country distribution

Figure 1: Geographical distribution of reporting formats



Figure 2: Cumulative number of active ICSRs in VigiBase

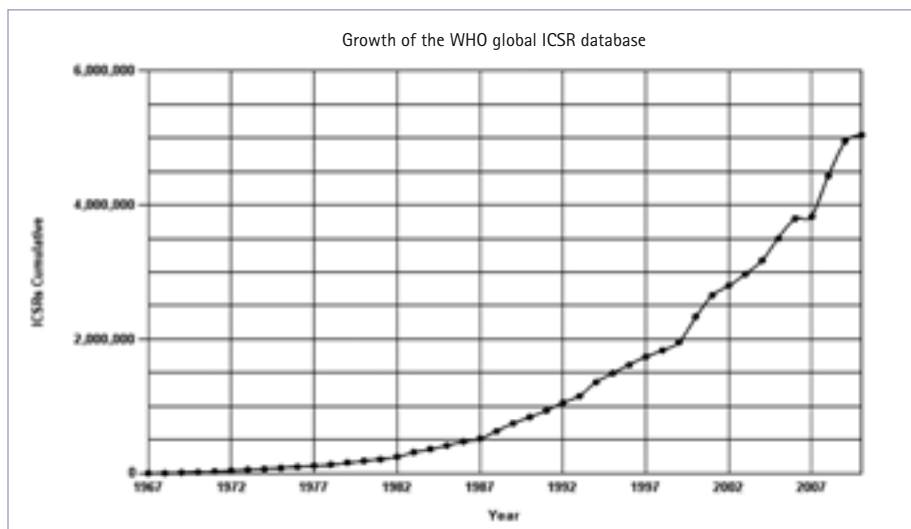
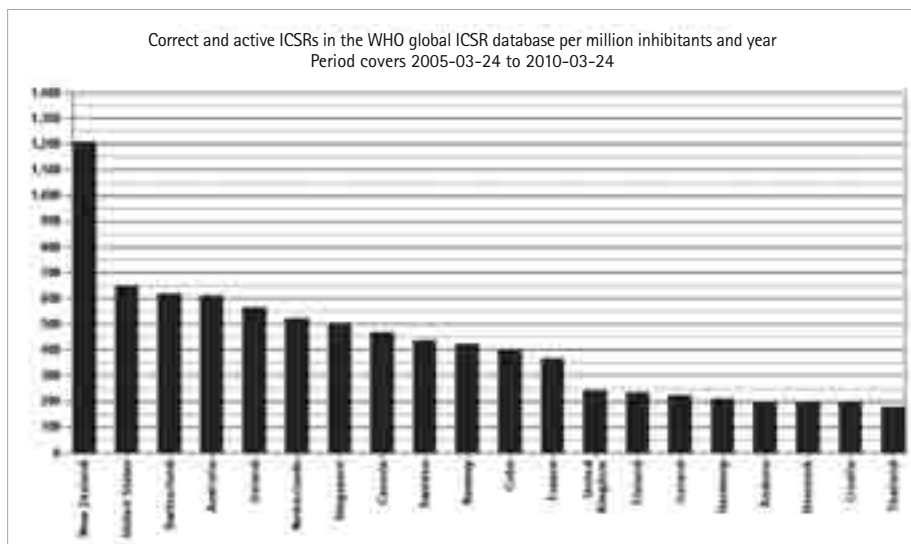


Figure 3: Reporting rates (per million inhabitants and year) to the UMC (March 2005 to March 2010)



...and more countries using the recommended format

Not only the number of ICSRs continues to increase, but also the number of countries using the recommended international ICH-E2B format (E2B) instead of the old WHO format (Intdis) is on the up.

In 2008, 43 countries used Intdis and 42 countries used E2B (including 21 countries using the UMC's VigiFlow reporting tool). During the last year a few more countries changed to the E2B format, and for the first time more countries are now using E2B instead of Intdis. As of March 2010, 39 countries still used Intdis while 48 countries were using E2B format (including 29 VigiFlow countries).

Twice-a-year statistics including the cumulative number of reports, the reporting rates, the country distribution and the submission frequency are published in Uppsala Reports and posted on the UMC website.

Cumulative reporting

Figure 2 shows the cumulative number of active ICSRs in VigiBase. The average yearly increase in number of ICSRs over the last five years has been approximately 350,000. During 2009 the UMC in fact received 515,997 ICSRs. As of March 4th 2010, the total number of active ICSRs was 5,035,141.

Figure 4: Country distribution of ICSRs in VigiBase as of March 2010 (total number of ICSRs approximately 5 million)

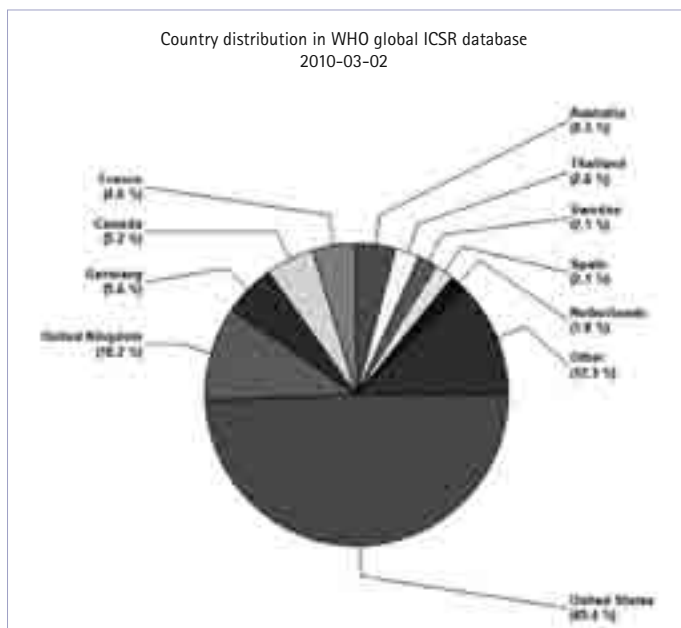
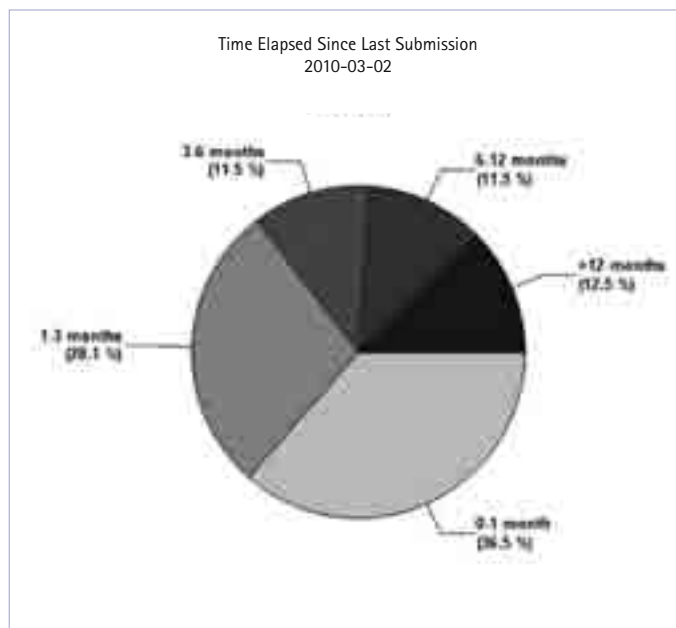


Figure 5: All WHO Programme members: time elapsed since last submission (proportion of countries as percentage) as of 2010-03-02



Submission frequency

WHO Programme member countries should submit ICSRs to the UMC on a regular basis, preferably once a month, but at least every quarter. This is important to keep VigiBase updated with the most recent safety information. During the last 12 months, only 47% of the member countries fulfilled the minimum criteria of submitting ICSRs at least every quarter.

As shown in Figure 5, approximately 65% of the countries have sent reports during the last three months. Although 12.5% of the countries have not submitted any reports during the last year, this figure is greatly improved since September 2009, when 21% had not submitted any reports in 12 months (see UR47).

European Economic Area (EEA) update

Since there has been a focus on European countries within EEA during the past year (situation analysis via a survey in September 2009, then follow-up), the UMC is pleased to share the positive outcome with the final two charts on this page. More than 85% of EEA countries have submitted reports to the UMC during the last three months (Figure 7). Only four countries (out of 27) have not sent any reports within three months. This is a huge improvement compared to same date last year, where only 44% had submitted cases within the actual quarter. As many as 9 countries (33,3%) had not submitted any cases for over a year the same period last year (Figure 6).

The main reasons for not complying with the requested frequency of ICSR submission to the UMC are technical issues with the extraction of reports or limitation of staff at the national centre.

Future plans

The UMC will continue to follow up on countries, in regions other than Europe, by performing situation analyses. We are always keen to hear about the kind of support/advice/help that national centres need from the UMC in order to comply with the reporting requirements. Any input/suggestions in relation to this matter are welcome! Send your comments/suggestions/dilemma to our general reporting inbox at vigibase@who-umc.org

Figure 6: EMA countries -time elapsed since last submission as of March 2009 (proportion of countries as percentage)

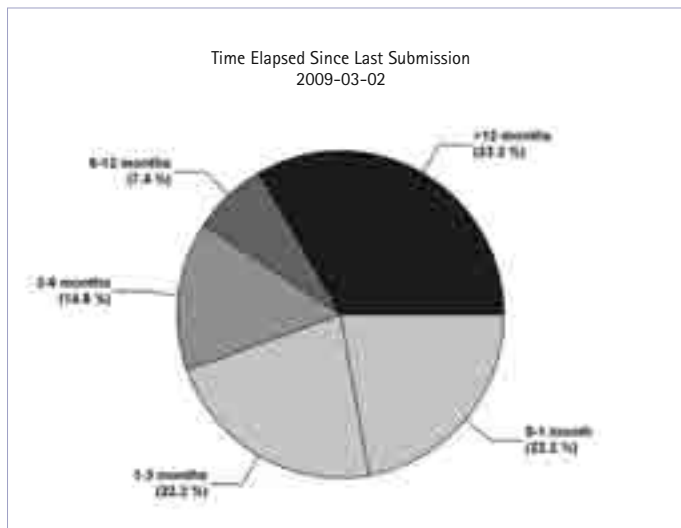
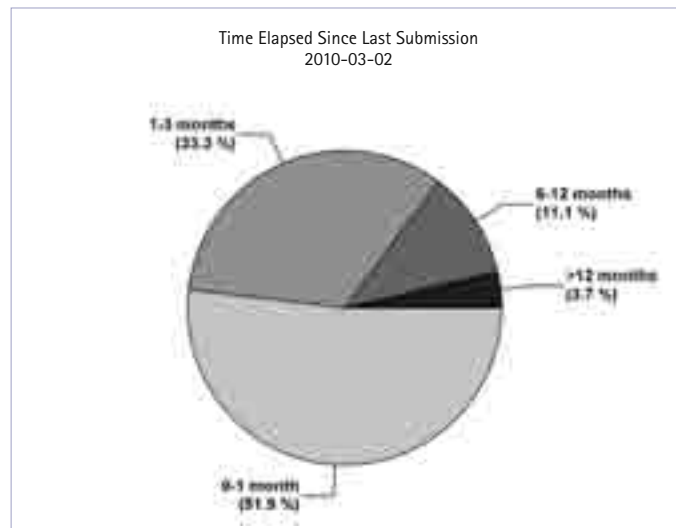


Figure 7: EMA countries - time elapsed since last submission as of March 2010 (proportion of countries as percentage)



Akwaaba – Welcome to Ghana

Geoffrey Bowring

As announced in the last Uppsala Reports, the 33rd Meeting of the WHO Programme for International Drug Monitoring will take place in Ghana. The provisional dates for the 2010 annual meeting, to take place in Accra, capital of Ghana, are 29 October to 3 November (including pre-meetings). National Centre heads will be receiving a questionnaire and official invitation from WHO Headquarters.

ISoP to follow

The National Centres meeting will be immediately followed by the first sub-Saharan African meeting of the International Society of Pharmacovigilance (ISoP) entitled *Pharmacovigilance in the global village*. ISoP will run from 3rd-6th November 2010 and full details can be found at their website www.isop2010.org. The chair of the scientific committee is Dr Brian Edwards.

The hosts are the Drug Evaluation and Registration Department of the Ghanaian Foods and Drugs Board.

A welcoming destination

Ghana is situated on the west coast of Africa, 750 km north of the equator and the neighbouring states are Burkina Faso, Côte d'Ivoire and Togo, with the Atlantic Ocean along the south of the country.

Sites of interest in Accra include Jamestown, the Independence Arch and the Nkrumah Museum. The ten regions of Ghana all offer

a variety of experiences for the inquisitive traveller, from the scenic beauty of the Volta region, the cultural heart of Ghana in Ashanti region with its festivals, national parks, and various sites particular to gold and diamond mines or cocoa production. Excursions to Cape Coast Castle and other nearby places of interest will be offered to WHO delegates during the programme.

Essential travel tips

- The official language of Ghana is English and the time zone is GMT.
- Ghana has a tropical equatorial climate (hot with seasonal rains) and November is normally dry, although tropical rainstorms sometimes occur.
- Ghana has a vibrant and free media, with 6 terrestrial TV stations and several newspapers.
- Credit cards are accepted in most hotels and major outlets, although it is advisable to have cash for day to day expenses. Money can also be withdrawn at the numerous ATM machines in Accra. Traveller's cheques are not popular in Ghana. The local currency is the Ghanaian cedi (GHS).
- Those with GSM phones can buy SIM cards for use whilst in Ghana.

International calls from Ghana using the cell phone are quite cheap at about 20 US cents per minute at peak times. Available networks are MTN, Vodafone, Tigo, Kasapa and Zain.

- Accra is one of the friendliest and safest cities in Africa; but as anywhere you do need to be aware of pickpockets and petty thieves especially around crowded areas like bus stops and markets. Always be willing to ask for assistance any time you face difficulties. Night life in Accra starts slowly but peaks around 11:00pm.
- Ghana's Accra International Airport receives airlines from many world destinations and direct flights to and from Europe include: British Airways (London), KLM (Amsterdam), Lufthansa (Frankfurt), Alitalia (Rome); and Ghana Airways, the national airline, flies to Rome, London and Düsseldorf.
- All visitors to Ghana are required to have a visa - except citizens of West African countries belonging to ECOWAS. A valid passport is mandatory.
- All visitors are required to show a valid certificate of immunization against yellow fever. Ghana is a malaria endemic country and non-immune visitors are strongly advised to take prophylaxis before arrival. Mosquito repellents can be obtained from local pharmacies and will be of use especially for outdoor activities and at night.



New Chair of UMC Board

Geoffrey Bowring

The operations of the WHO Collaborating Centre for International Drug Monitoring (the Uppsala Monitoring Centre) are governed by an agreement between WHO and the Swedish government. The Centre, established as a Swedish foundation, has an international Board where WHO appoints three members and three others are appointed by the Swedish government.

Mr Carl Älfvåg recently concluded his term as Chair, and his place has been taken by the distinguished Swedish doctor, Anders Milton.

Introducing Anders Milton

Born in 1947, Anders Milton is a well-known figure in Sweden. After graduating as a medical doctor and PhD he served as a clinician at the Department of Nephrology at the Academic hospital in Uppsala. Among the many positions he has held in his career may be mentioned President and later CEO of the Swedish Medical Association, Chairman of the council of the World Medical Association (WMA), President of the Swedish Confederation of Professional Associations (SACO), and President of the Swedish Red Cross. He has been the leader of many Swedish governmental investigations, e.g. on the psychiatric services, the effects of activities regarding

HIV/AIDS, and prevention against unwanted pregnancies. He has been an advisor to the Swedish Delegation to the World Health Assembly on several occasions and chair of the drafting group at the Assembly three times. In addition, he has been engaged in work in support of human rights, legal systems applicable to warfare, and ethics of medical practice.

Anders accepted to become the chairman of the UMC Board because he wants to promote good and safe healthcare, and safe and effective pharmacotherapy is an important part of that. The UMC is delighted to welcome Anders as Chair of the Board.

Other new faces

Other members appointed by the Swedish Government are Assistant Professor Ellen Vinge, Clinical Pharmacologist, County Council of Kalmar and Annika Alström, Information Director at Kronans Droghandel, a Swedish pharmacy chain. Thomas Bradley, Clinical Pharmacologist, Linköping University Hospital and Johanna Adami, Associate Professor and Head of the Department of Biotechnology, Vinnova, Stockholm are alternates/deputies appointed by the Swedish government.



Anders Milton

WHO has nominated Dr Lembit Rägo (alternate currently vacant) from WHO headquarters, Dr June Raine from the UK's national medicines regulatory agency MHRA (alternate Dr Norbert Paeschke from the German Medicines Control Agency, BfArM), and Professor Mohammed Hassar from the Moroccan Institute of Hygiene (alternate Dr Rachida Soulaymani-Bencheikh, the Moroccan pharmacovigilance centre).

The Board meets three times per year in Uppsala.



Members of the new board at the UMC offices in March, from left to right: Mohammed Hassar, Annika Alström, Anders Milton, Marie Lindquist (Director of the UMC), Thomas Bradley and Norbert Paeschke

Monitoring Medicines takes off

Sten Olsson

A major international project, with the full title 'Optimizing drug safety monitoring to enhance patient safety and achieve better health outcomes' has recently been launched.

The project – under its short name 'Monitoring Medicines' – was briefly presented in Uppsala Reports 47, page 14. It is funded by the European Commission (Seventh Framework Programme (FP-7) of the Research Directorate), and is aiming to improve patient safety both within countries of the EU and in other regions. The project will run for 3½ years. Project partners cover a wide range of organizations dedicated to improving public health through safer use of medicines. The project is coordinated by the UMC with WHO Headquarters as the main partner and nine other partners (see box).

Monitoring Medicines project partners

- The Uppsala Monitoring Centre
- WHO Headquarters
- Copenhagen HIV Programme, Denmark
- University of Ghana Medical School
- Pharmacy and Poisons Board, Kenya
- Centre Anti Poison et de Pharmacovigilance du Maroc
- Lareb, Netherlands Pharmacovigilance Centre
- Zuellig Family Foundation, the Philippines
- Medical Products Agency, Sweden
- Elliot Brown Consulting Ltd, UK
- National Patient Safety Agency, UK

In the first week of March, representatives of all the collaborating partners gathered in Uppsala for a 2-day meeting hosted by the UMC, to plan the work in each section of the project that they will be involved in, and to understand each other's professional background and commitment to the project.

Concepts and objectives

The Monitoring Medicines project has four objectives:

1. to support and strengthen consumer reporting of suspected ADRs
2. to expand the role and scope of national pharmacovigilance centres to identify, analyze and prevent medication errors

3. to promote better and broader use of existing pharmacovigilance data for patient safety
4. to develop additional pharmacovigilance methods to complement data from spontaneous reporting systems.

Consumer reporting

A review of direct consumer reporting practices of suspected ADRs in about ten countries, where consumer reporting is already in place, will be carried out. The results of the review will be used as the basis of recommendations of best practices for consumer reporting.

An expert group including representatives from consumer organizations will be supported to prepare a guideline for consumer organizations on reporting of ADRs.

UMC will adapt its data management tool VigiFlow to receive, store and manage consumer reports. Through the new version of VigiFlow some consumer reports would also be automatically transferable to national centre databases and to the WHO global ICSR database, VigiBase.

Lastly, WHO will organize two workshops, to train consumer organizations in applying the reporting guideline to promote collection of consumer reports and using the new reporting tool.

Medication errors

The 'Identifying, analysing and preventing medication errors' section of the project aims at encouraging national pharmacovigilance centres to expand their activities to learn more from existing data through:

- collection of information on adverse events relating to drug prescribing, dispensing and administration, and
- analysis of these data, and international dissemination of the findings.

Ten national pharmacovigilance centres will be trained to identify medicines that are frequently associated with safety risks and by root-cause analysis of identified reports explain why adverse events related to the use of the medicine occurred. By learning from this analysis, preventive measures can be suggested to health care providers.

The Moroccan pharmacovigilance centre, which has long-term experience in monitoring medication errors, will collate the results of data analysis from the ten centres. In collaboration with the National Patient Safety Agency, UK, they will produce a guideline describing how to undertake step-by-step analysis of data describing medication errors contained in national pharmacovigilance databases.



Work session for the Monitoring Medicines partners

Better use of existing data

The focus of the 'Better use of existing pharmacovigilance data for patient safety' section of the project is to analyse global pharmacovigilance data through advanced data-mining to better identify medicines with dependence liability and medicines of substandard quality. Data-mining uses advanced statistical methods for identification of patterns in large databases. The research team at the UMC will identify indicators of dependence liability, using the ICSR data in the WHO ADR database.

The same research team will also use data-mining techniques to analyse the more than 100,000 reports in the WHO database that are recorded as 'treatment ineffective', as a possible indicator of substandard medicines. Preliminary investigations suggest that at least some of these reports may be due to substandard and/or counterfeit products. Possible explanations, other than substandard medicines, will be reviewed. The reports for which therapeutic inefficacy is suggestive of substandard medicines will be further analysed, and resulting patterns reviewed and classified.

Additional methods for pharmacovigilance

Throughout the world, spontaneous reporting is the most common surveillance method used. It is the easiest to establish and the cheapest to run, but reporting rates are generally very low and subject to strong biases, and there is limited knowledge of overall drug use. These factors hinder accurate and timely assessment of risk rates and comparisons between drugs.

The Monitoring Medicines project will develop tools to facilitate and expedite the characterization of early signals identified through regular spontaneous reporting, by focusing on problems with an explicit case definition. The main emphasis will be on methodological development in active follow-up of exposed patients and particularly Cohort Event Monitoring (CEM).

Guideline and manuals on the principles and practical accomplishment of focussed spontaneous reporting and CEM will be produced. WHO will organize four regional workshops for nine countries to introduce the guidelines and to pilot its adaptation and implementation for meeting disease-specific pharmacovigilance objectives. Pharmacovigilance centres will collect reports of adverse events in patients treated with medicines for HIV/AIDS or malaria, using active and focussed surveillance methods in which they were trained in the workshops. Based on the experience from the pilot of the



Representatives of all the Monitoring Medicines collaborating partners outside the Uppsala Monitoring Centre office building

guidelines, they will be further refined, then published and disseminated to countries participating in the WHO Programme for International Drug Monitoring.

UMC will develop software for managing adverse event reports collected through active surveillance and focussed reporting.

Support to health workers treating HIV/AIDS patients

A pilot pharmacovigilance database, separate from the database mentioned above, will be organized by merging ADR data on anti-retroviral medicines from several sources, into a common database. A user-friendly web-based query tool will be created to enable healthcare workers to search and retrieve information contained in the database.

A web-based distance learning tool to train and assist healthcare workers in evaluating the ADR information retrieved, and a risk score calculation tool, to allow evaluation of ADR development based on clinical data, will also be produced.

Dedicated website

The progress of the Monitoring Medicines project will be reported periodically on a designated project web site www.monitoringmedicines.org which will have a link from the normal UMC site.

Behind what you see on your screen

Bruce Hugman

At the back of familiar, everyday things – newspapers, mobile phones, TV – there's always an invisible team of clever people who make it all happen and keep things going. That's true, too, for VigiBase, VigiFlow, the WHO Drug Dictionary (WHO-DD), VigiSearch, PaniFlow and all the rest of UMC's portfolio of products, which thousands of people round the world see on their screens and use every day.



One of Senior Specialist Sven Purbe's tasks is to develop automatic recognition of drug names in reports. As you can see from the lists in the box opposite, a single drug or procedure may be reported in spellings which are very varied and, some, hardly recognisable at all. The number of reports makes manual interpretation impossible. When Sven is not wrestling with such complex technical problems at work, out of hours he's maybe enjoying a piece from his enormous collection of classical Western music, or demonstrating his speed and agility on the badminton court (or at the pool table).

In UMC's case, the backroom team is known as Production, Development and Quality – PDQ! for short, not least because tight deadlines are a regular feature of their lives. That there's a more or less permanent team of sixteen people is an indication of just how extensive and complex the work is and how seriously UMC is committed to it.

Serious skills and lots of tasks

Production leaders, IT-architects, system developers, database experts and quality co-ordinators form the basis of the

team. Amongst many other tasks, they are responsible for the production activities which result in accurate up-to-date tools and resources on users' desks: quarterly updates of WHO-DDE² (a full month's work for six people each time); inputting, documentation grading and quality assurance of ICSR³ data entry (roughly 75,000 new reports each month, and for each quarter validation of between 600 and 800 ascii-text files manually, checking content, format, etc); upgrading DD Browser information and VigiSearch data, and lots more. They also participate in the complex GxP quality assurance processes for VigiFlow and the DD Browser.

Then, behind all that, are the systems and tools which make it possible: the development of software packages for reporting and data management: VigiFlow and PaniFlow, for example, developed in collaboration with Swissmedic; VigiMine the user-friendly data mining tool, DD Browser, and so on.

"Our job," says Johanna Eriksson, PDQ's manager, "is to make sure the whole portfolio of UMC products is accessible and effective for our users round the world. While we constantly maintain and improve existing tools and resources and meet our production deadlines, we're also responsive to requests for improvements and entirely new packages – PaniFlow and CemFlow⁴ being recent examples. We're a very busy team!"



Bo Östling has worked with ADR data systems for 32 years. When asked how he's stayed loyal for so long, he says, "It's a good place to work." Bo is known as the 'Brewmaster' because he has a comprehensive knowledge of almost every variety of beer sold in Sweden (and some abroad, too). Not drinking beer at all until six years ago, he started when he was searching for attractive bottles to store his home-made herbal snapps, and one beer brand was sold in just the bottle he fancied. Rather than pour the beer away, he tried it and liked it, and so started on his journey to being a connoisseur. (His recommendation, by the way, is for Belgian style beer, or those known as 'Abbey' style from their origin in monastery brews.)

When the magnetic tapes came from Geneva...

Bo Östling, system developer, has been associated with UMC data since 1978, when he was appointed by the Uppsala University

Data Centre (UDAC) to process the raw ADR data which had been collected at WHO headquarters in the early days of the Programme for International Drug Monitoring. Uppsala University had the (massive) hardware and the engine to develop a new kind of relational database, known as MIMER. Bill Dagérus was around in the earliest days with Bo, while Björn Moberg, Stefan Lewenfalk, Magnus Wallberg and Johanna Eriksson – all current members of PDQ, joined UMC earlier this decade. Bo remembers the heavy discs of those days, storing 100MB and 600MB of data, and all the problems of access and priority on the much-in-demand equipment⁵.



For reasons that are not entirely clear, PDQ have a dominant presence at the UMC pool table where, no doubt, their complex minds are able to relax and develop novel answers to questions about software systems and the meaning of life. Mats Jonsson, Thomas Vidinghoff, Bill Dagérus, Björn Moberg, Bosse Östling watch Sven Purbe prepare a winning shot.



Jessica Nilsson (seen here with systems developer Stefan Lewenfalk), is team leader for everything relating to VigiBase (5 million reports and all) and Nike Meder (on holiday when our resident photographer called) is production leader for the Drug Dictionary (the basic WHO-DD with 70,000 entries and WHO-DD Enhanced with 1.8 million entries). Both trained as pharmacists but moved over to their current areas of highly specialised technical work.

How things have changed!

The original IBM 370 main frame has given way to much more sophisticated server equipment as for example a HP (Hewlett Packard) DL580 G5 4 x 6-Core with a total disk capacity of 3.5 TB used for complex calculations of IC values etc, and has reduced the processing time from several days into hours. MIMER has been replaced by MS SQL 2008 as the database engine, and VigiBase has grown into the world's largest global collection of ICSRs.

In the seemingly relaxed and cheerful mood of the UMC PDQ team, remarkable things are achieved.

Did you mean...?

Medicines and procedures come in so many varieties in the ICSRs received that intelligent word-recognition software is essential to make sure the many variants are thoroughly (and automatically) assessed, decoded and accurately recorded. Here are lists of the variants for two common items recently taken from the records.

Which drug is it?

Injection	Acetylsalicylic
Ijection	Acetyl salicylic
Inection	Acetysalicylic
Inejction	Acetylsalidic
Injection	Acethylsalicyl
Injection	Acetylalicylic
Injcton	Acetylasicylic
Injection	Acetylsalicylic
Injection	Acetylsaicylic
Injcton	Acetylsalicyc
Injection	Acetylsalicytic
Injecfion	Acetylsalicycyclic
Injectin	Acetylsalicylic
Injectino	Acetylsalicyc
Injection	Acetylsaliylic
Injectoin	Acetylsaliyyclic
Injection	Acetylsaliylic
Injedtion	Acetylsalylic
Injection	Acetylsaicylic
Injection	Acetylsicylic
Injctcion	Acetysalicycyclic
Injettion	Actylsalicylic
Injction	Acetylsaliyl
Lnjection	Acetylsalicyclic
	Acetysalicylic
	Acetysalicylic
	Aetylsalicylic
	Acetyl Salicylic
	Acyetlsalicylic



PDQ Manager, Johanna Eriksson joined UMC in 2004, after being test leader and then project leader for improvement of the web version of the publication that provides detailed and easily-accessible information about all the medicines available in Sweden - FASS. (UMC uses this as one of the validation sources for data about medicines in Sweden.) Her recreational escape from data and motherhood is horse-riding.

Thanks to Johanna and team members for help in writing this article, and to Magnus Wallberg (moose-hunter) for the photos.

- 1 In some parts of the world 'PDQ' is commonly recognised as the abbreviation of 'Pretty Damn Quick' – a more or less polite way of telling people to move quickly and finish the job.
- 2 WHO Drug Dictionary Enhanced
- 3 ICSR – Individual Case Safety Reports, this is the definition to replace Adverse Drug Reaction (ADR) reports proposed by ICH (International Conference on Harmonisation)
- 4 PaniFlow is the reporting and management tool developed for use in A/H1N1 and other mass vaccination programmes; CemFlow is a data capture and management tool for use in cohort event monitoring (CEM).
- 5 Björn Moberg kindly provided details of the earliest hardware which we hope may interest some readers with that kind of specialist interest. From 1972 a computer named IBM370/155 was used at UDAC. This computer, with time sharing and multi-tasking features, had a RAM of 512MB and four switchable disc memories with a capacity of 100MB each. The operating system used was called MVT (Multitasking with Variable number of Tasks). At the end of the 1970s a new (second-hand) computer, IBM370/158 and an IBM compatible BASF computer using virtual memory technique were obtained. This was the time when the database management system, MIMER was developed at UDAC – and was used in UMC systems until a couple of years ago.

Celebration and Change at CIOMS

Marie Lindquist

60 years of CIOMS

The Council for International Organizations of Medical Sciences (CIOMS), an international, non-governmental, non-profit organization, was established by WHO and UNESCO in 1949 – thus it celebrated its 60th anniversary last year. Through its membership, CIOMS is representative of a substantial proportion of the biomedical scientific community. By 2009 over 60 international, national and associate member organizations, representing many of the biomedical disciplines, national academies of sciences and medical research councils were affiliated. The main objectives of CIOMS are:

- to facilitate and promote international activities in the field of biomedical sciences
- to maintain collaborative relations with the United Nations and its specialized agencies WHO and UNESCO
- to serve the scientific interests of the international biomedical community in general.

New Head

Dr Gottfried Kreutz retired from his position as Secretary-General of CIOMS early in 2010 and has been replaced by the Swedish medical scientist, Dr Gunilla Sjölin-Forsberg. She was Head, Department of Drug Safety at the Swedish Medical Products Agency, and has been a member of CIOMS since 2007, participating in CIOMS Group VIII on application of signal detection in pharmacovigilance. The President of CIOMS is Professor Michel B Vallotton.

Bio-ethics

CIOMS has produced guidelines for the application of ethical principles in various key areas. These include the 1993 International Ethical Guidelines for Biomedical Research Involving Human Subjects (in conjunction with WHO). In 1999-2002 these Guidelines were revised and updated, and in 2002 CIOMS published the new text of the International Ethical Guidelines for Biomedical Research Involving Human Subjects (CIOMS website www.cioms.ch/frame_guidelines_nov_2002.htm). Translations of the Guidelines have been made into French, Spanish, Portuguese, Chinese, Japanese, Korean and Vietnamese.

Safety reports

In the early 1980s a series of reports on a broad range of drug safety topics was initiated by CIOMS via working groups.

CIOMS I (1990, International Reporting of Adverse Drug Reactions) included the CIOMS I reporting form for standardized international reporting of individual cases of serious, unexpected adverse drug reactions. CIOMS II, III and IV concerned Periodic Drug Safety Update Summaries and Core Clinical-Safety Information on Drugs. CIOMS V (Current Challenges in Pharmacovigilance: Pragmatic Approaches, 2001) was set up in 1997 to consider the most important elements that need to be taken into consideration in dealing with drug safety of post-marketed drugs.



*Gunilla Sjölin-Forsberg,
Secretary-General of CIOMS*

The CIOMS Working Group on Pharmacogenetics looked at drug development and regulatory, ethical, educational and economic issues related to pharmacogenetics. Its final report 'Pharmacogenetics – Towards Improving Treatment with Medicines', was published in 2005.

Since 2003 there has been a CIOMS Working Group on Standardised MedDRA Queries (SMQs), consisting of senior scientists from regulatory authorities and pharmaceutical companies, the MedDRA Maintenance and Support Service Organisation (MSSO) and WHO. In 2004, a report, 'SMQs – Development and Rational Use of Standardised MedDRA Queries (SMQs)', was published.

CIOMS VI, established in 2001, considered issues related to the surveillance, assessment and reporting of drug safety data from clinical trials. The report by 12 senior scientists, 'Management of Safety Information from Clinical Trials' was issued in 2005.

The CIOMS VII Working Group on 'Development Safety Update Report (DSUR)' considered the rationale, format and content of a periodic development safety update report to inform drug regulatory authorities on safety findings of new medicines during their developmental research. The report was published in 2006.

A Joint CIOMS-WHO Working Group on Drug Development Research and Pharmacovigilance in Resource-Poor Countries published recommendations in 2006.

At the request of WHO, in 2005 a 23-member CIOMS/WHO Working Group on Vaccine Pharmacovigilance was created to develop general definitions and contribute to the development, review, evaluation and approval of definitions on adverse events following immunization.

Reporting and Terminology of ADRs

This project involving 120 experts defined over 180 terms during 16 working meetings; in 1999 a cumulative volume entitled Definitions and Basic Requirements for the Use of Terms for Reporting Adverse Drug Reactions and a corresponding CD-ROM were published.

CIOMS and the UMC

CIOMS provides an excellent forum for exchange of ideas and scientific discussion in areas where international harmonization is desirable and possible. Over the years, the UMC has been represented in many CIOMS working groups, on topics where we have expertise.

The latest, CIOMS VIII, established in 2006 and preparing a consensus report on the development and application of quantitative methods for signal detection using pharmacovigilance databases, concerns an area where UMC has done pioneering research and development since the mid-90s, and where we believe our input has been useful.

To Gunilla, our congratulations on your new post! You have been an important contributor to pharmacovigilance for many years, and we look forward to continued close collaboration between CIOMS and the UMC.

Worldwide PaniFlow programme

Jerry Labadie

WHO is coordinating the distribution of donated A/H1N1 pandemic influenza vaccines to 95 low- and middle income countries. Distribution is now underway (deployment updates may be found at <http://www.who.int/csr/disease/swineflu/action/en/index.html>). These 95 countries are also being offered PaniFlow free of charge to monitor safety during their national immunization campaign.

PaniFlow is the UMC's web-based vaccination adverse event reporting tool based on VigiFlow, which is now widely used throughout the world (see UR47). It has been developed in close collaboration with Swissmedic, the national regulatory authority in Switzerland.



A/H1N1 pandemic influenza vaccines arriving in Mongolia, January 2010 (photo copyright WHO)

Using PaniFlow to monitor safety during the immunization campaign with pandemic influenza vaccines is an excellent opportunity for national centres to get hands-on experience with a web-based reporting tool. Safety monitoring during the national immunization campaign also offers opportunities to the national pharmacovigilance and the immunization programmes to join forces and strengthen collaboration.

Cohort Event Monitoring and CemFlow

A new vital safety method and a tool to support it

Magnus Wallberg



Magnus Wallberg, John Liddy, Monica Plöen, Anders Viklund, Micheline Diepart, Ralph Edwards and Ihor Perehinets, planning CEM monitoring of ARVs in Uppsala

An introduction to CEM and CemFlow

Cohort Event Monitoring (CEM) is a method where information is collected, with the focus on events, for 'all' patients in a cohort being treated with a medicine, group of medicines or a substance. The cohort should be selected without biases from all patients being treated with the monitored medicine, and the events should include also incidents, not only Adverse Drug Reactions (ADRs). Some, but not all, of the goals with this data collection are to produce risk profiles, find new signals and to assist in elaborating recommendations for safer use of the medicine, aiming at better safety for the patient.

CemFlow is a data management tool developed and maintained by the UMC. The tool is built to collect and analyze data from CEM programmes. CemFlow is web-based and hosted by the UMC in Uppsala.

CemFlow has been available for about one year, but so far has been primarily focused on monitoring anti-malarials.

Recent activities

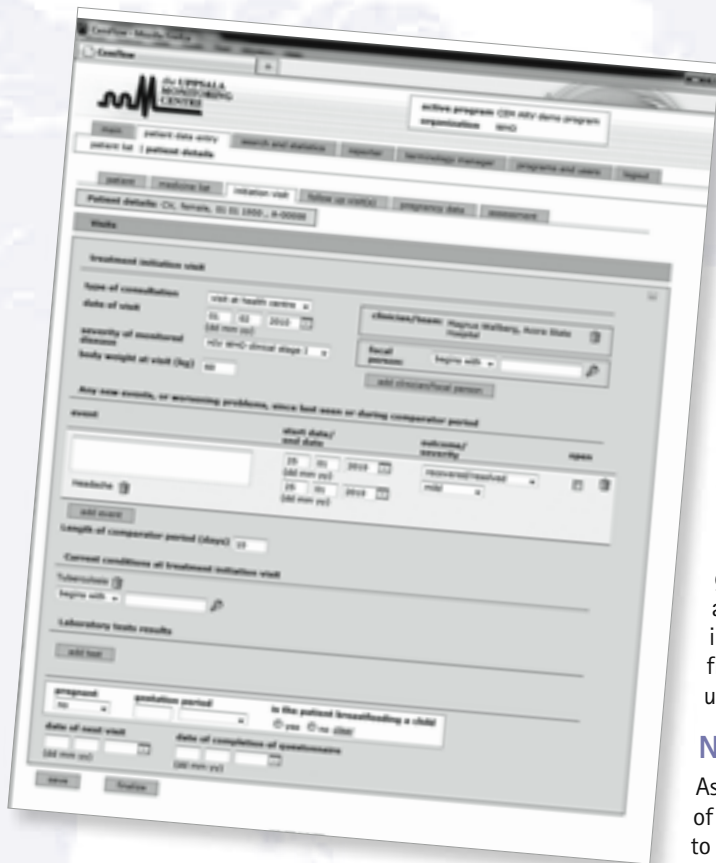
With the training course in Dar es Salaam, Tanzania, in November 2009 (see UR48 p7)

the development of the CemFlow software had a real injection of energy. It became apparent from the discussions at that meeting that some changes were needed, both in the set-up of a CEM programme and in the CemFlow tool to support the more complex demands of collecting data regarding ARVs compared with malaria.

To start with, a few telephone meetings were held focused on getting as much done before an HIV meeting in Accra, Ghana, in January. After the Ghana meeting, activities were increased even more (see next section) to be able to present the modified version in Geneva at the Project Advisory group Meeting for Pharmacovigilance for Antiretroviral Medicines that was arranged at the beginning of March.

The development of the 'ARV adjusted' CemFlow has now been finalized. The new version has been designated the version number 2.0. Version 2.0 of CemFlow was released the 16th of April.

In order to avoid confusion, version 2.0 of CemFlow can still be used for monitoring anti-malarials. There is not – and hopefully there will never be – different CemFlow versions for different monitoring scenarios.



The initial patient visit entry page in CemFlow

WHO HIV meeting in Uppsala

To be able to define what to change and why, but also to clear up misunderstandings and get a common view, a face-to-face meeting with the project team was arranged in Uppsala. This took place on the 25th and 26th of January during some cold Swedish winter days. Participating from the WHO were

Micheline Diepart, John Liddy and Ihor Perehinets. UMC was represented by Ralph Edwards, Monica Plöen, Anders Viklund and Magnus Wallberg.

The meeting was very good and constructive, and the ideas and discussions very much helped to improve the whole CEM methodology, not only for ARV monitoring, but also the way CEM is supported by the CemFlow tool in general. Much effort was also put into making the interface more user-friendly and intuitive to use.

New in CemFlow 2.0

As already mentioned, lots of work has been carried out to make the user interface more intuitive and easier to

work with. Related data fields have been collected in separate screens to avoid scrolling as far as possible, and a new menu system has been implemented. User guides have also been developed. There are now several different user guides available and the access to these restricted, so that each user of the system may only get access to guides relevant for his/her work.

The Search and Statistics capabilities of CemFlow are also very much improved with new and better stratification possibilities and better listings of patients and their events. There is also an entirely new statistical section with administrative statistics, enabling the administrators of the CEM program to get a better overview about key features of the data collection.

Next steps

There are still a few outstanding issues in the CemFlow tool. One of these is a module to collect pregnancy data, but there are also additional statistical and data export functions needed. Graphical output of statistical data is another feature that has been requested.

Although there are some missing pieces, the tool is available for use. There is a need to get data entered into the system so as to fine tune data entry screens and also to evaluate existing statistical functions and identify the need for any other function, not in the tool today.

If you have questions about CEM or CemFlow, please do not hesitate to contact the UMC or WHO for further information.

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(monica.ploen@who-umc.org)

WHO contact person: Shanthi Pal
(pals@who.int)

Community monitoring in Namibia

Assegid Mengistu

A valuable study entitled 'Piloting community-based medicine safety monitoring in public health treatment programs in Namibia' was carried out last year.* Since 2008 the trend of reporting of ADRs in Namibia seems to be increasing, but is still far from the optimum number of 400 ADR reports per year required for Namibia (based on the WHO empirical standard of 200 ADR reports / million inhabitants / year). A programme was piloted to involve Community Health Workers (CHWs) in two regions of Namibia where monitoring of medicines used in TB/HIV programmes was taking place.

A 2-day basic medicine safety monitoring orientation training was conducted for 66 CHWs from the two regions using simplified ADR terminologies and definitions and a simplified reporting form.

Improvement in knowledge

In the awareness and knowledge of CHWs on the importance and need for early reporting and management of suspected adverse effects of ARVs and anti-TB medicines an improvement was noted in pre- and post-training tests – from scores ranging from 27% to 100% pre-training to 64% to 100% for the post-test. The mean score for the pre-test was 72% compared to 82% for the post-test. In addition, 66% of the trained CHWs were able to correctly complete the ADR reporting form, although few did so in the pilot.

CHWs have untapped potential of playing an important intermediary role in enhancing community-based medicines safety monitoring in developing countries. Existing management supervisory channels for the

CHWs can be incorporated as reporting mechanisms especially when supported by simple, clear instructions and assisted by managers at health facilities. The pilot is still on-going and further follow-up is required to ascertain the effectiveness of the role of CHWs in reporting side effects of HIV, TB and other medicines used in the public health programmes.

*Authors: Assegid Mengistu¹, Evans Sagwa², Elena Moreno³, Johannes Gaeseb¹, Jennie Lates¹, Dinah Tjipura¹, David Mabirizi², David Novak³, Jude Nwokike².

- 1 Ministry of Health and Social Services, Namibia;
- 2 Management Sciences for Health/ Strengthening Pharmaceutical Systems;
- 3 Medicos del Mundo

Uppsala team Travels West

Elki Sollenbring

The Pan American Health Organization (PAHO)/WHO in co-operation with the Central American Integration System (Sica) and the Ministry of Health of Costa Rica recently invited the UMC to carry out a pharmacovigilance training course for Central American countries and the Dominican Republic.

Seven countries in attendance

The training course was held in San José, Costa Rica from 1–5 February 2010. It was attended by around 25 participants from seven countries: Costa Rica, Nicaragua, El Salvador, Guatemala, Panama, the Dominican Republic and Mexico. The countries are already organized in a technical sub-regional committee of medicines and work hard to develop strategies to ensure quality, safety and efficacy of medicines in the region.

The Vice minister of Healthcare Dr. Ana Cecilia Morice Trejos opened the course. She was accompanied at the front table by Federico Hernandez representing PAHO/WHO, Sten Olsson and Richard Hill from the Uppsala Monitoring Centre and Maria de los Angeles Morales from the Costa Rican Medical Product Agency.



Seven central American countries were represented

Regional drug safety

The intention of the course was to improve the pharmacovigilance systems in the region. Some of the countries, Costa Rica, Guatemala and Mexico, have had an established pharmacovigilance system for many years, but others have only recently started. The course covered all aspects of pharmacovigilance from basic concepts to a discussion on how to promote the further development of pharmacovigilance systems in Central America.



Participants working on the course in San José

Local and UMC speakers

Most sessions were facilitated by UMC representatives but very important contributions were also made by Indira Credidio of the Pharmacovigilance Centre of Panama who gave an overview of Panama's pharmacovigilance experience and the future of the programme, and Marielos Campos from the Ministry of Health of El Salvador, who presented the general programme of the Technical sub-regional committee of medicines.

Sten Olsson talked about the need for pharmacovigilance, spontaneous adverse reaction reporting, medication errors and patient safety, communicating drug safety issues with other partners and the role of the pharmaceutical industry in pharmacovigilance. He also led a working group on the future pharmacovigilance system for Central America.

Richard Hill spoke on the spectrum of drug related health problems, safety monitoring of vaccines, identifying early signals of drug problems, other methods used in post-marketing surveillance, etc. Causality assessment was a very important part of the training. After Richard's presentation on the subject, participants were divided into working groups to discuss causality assessment of real case reports.

Elki Sollenbring talked about how to establish a pharmacovigilance centre, the WHO Adverse Reaction Monitoring Programme, the optimal national centre in

the WHO network, safety monitoring of traditional medicines, etc. She also gave an introduction to VigiFlow and led a hands-on session on the use of this tool. Participants expressed their satisfaction with VigiFlow being available in an all-Spanish language version.

Remote lectures

Lecturers were also brought in from WHO Headquarters, Geneva, through recorded presentations available on the internet (<http://media.medfarm.uu.se/flvplayer/umc09>). Accordingly, Shanthi Pal's presentation on 'Pharmacovigilance in public health programmes' and Amor Toumi's presentation on 'Patient safety problems associated with counterfeited medicines' were shown. These presentations were originally recorded at the UMC pharmacovigilance training course in May 2009.

This was the first UMC pharmacovigilance training directed to this region. Having access to a native Spanish speaker from the UMC with a background in the region (Elki Sollenbring) and an excellent service for simultaneous translation contributed to the success of the event. The enthusiasm and professionalism of the participants and their desire to learn and benefit from the services of the WHO Programme was encouraging. The UMC will follow up this training activity and continue supporting the participating countries in their endeavour of building better systems for patient safety.

UMC at work in Thailand

Bruce Hugman

A day at the Thai FDA

During a trip to south-east Asia in January, UMC Director Marie Lindquist and Medical Advisor Rafe Edwards were invited to meet the Thai pharmacovigilance team and the signal detection advisory group for a day of discussion and training.

Ms Wimon Suwankesawong, head of the Health Product Vigilance Centre (HPVC), introduced the work of the centre and Ms Sareeya Wechwithan described the Thai signal detection process. Dr Woranee Bunchuailua, from Silpakorn University, presented a very elegant piece of research comparing the effectiveness of reporting odds ratio and BCPNN analysis for revealing drug-ADR associations in the Thai ADR database (her abstract appears in the box on this page).

The rest of the day was spent in workshop sessions examining the complexities of signal detection, risk management and risk communication, with UMC communications consultant, Bruce Hugman, joining in the last session.

With more than 300,000 reports in their database, over 30,000 new reports annually, and limited resources, the HPVC team was keen to explore how they could maximise the usefulness of the data, generate good information and detect signals effectively.

Comparing the effectiveness of ROR and BCPNN

Waranee Bunchuailua, BPharm, PhD candidate
 Prof. Ilene H Zuckerman, Pharm D, PhD
 Assoc. Prof. Vithaya Kulsomboon, PhD
 Wimon Suwankesawong, BSc (Pharm), MA
 Assoc. Prof. Pratap Singhasivanon, MBBS, DTM&H (Bangkok), DrPH (Epidemiology), MPH;
 Asst. Prof. Jaranit Kaewkungwal, PhD.

The study aimed to compare performance between the reporting odds ratio (ROR) and the Bayesian Confidence Propagation Neural Network (BCPNN) methods in identifying serious adverse drug reactions (ADRs) using the Thai FDA spontaneous database. The two methods were retrospectively applied to identify new, serious ADRs reported with antiretroviral therapy (ART) drugs using the dataset between 1990 and 2006. We plotted the ROR and the Information component (IC) against time to compare the differential timing of signal detection and the pattern of signalling over time between these methods. The ROR and the BCPNN methods identified the associations between ART drugs and serious ADRs at the same time. Both methods were similar in detecting the first signal of a potential ADR. However, the pattern of signalling seems relatively different with each method. Additional analyses of different drugs, ADRs and databases will contribute to increase understanding of methods for postmarketing surveillance using spontaneous reporting systems.

Industry training

The following day, at the invitation of PReMA (the Thai Pharmaceutical Research and Manufacturers Association) and the Thai FDA, Marie and Rafe provided a day's teaching on signal detection, risk identification, assessment and minimisation for about eighty participants, including the HPVC team and other FDA specialists. The

main purposes of the event were to provide opportunity for pharmacovigilance personnel in the public and private sectors to update their knowledge, to share and debate practices and to enhance their collaboration in pharmacovigilance. The afternoon session used real-world cases for discussion of signal detection, causality assessment, and processes in decision-making.

Dr Pravich Tanyasittsunorn, J & J's Medical Director in Thailand and the Philippines, and organiser of the event, expressed his earnest hope that the public and private sectors could work productively together. He also recorded his gratitude to the visiting UMC team for the excellence of their teaching.



The hardworking Thai FDA HPVC team

Erice Statement 2009: communication, medicines and patient safety

Twelve years after the original Erice Declaration, this current statement was also prepared in Erice, by an international group of volunteer professionals, representing themselves, and drawn from a broad range of stakeholder interests.

The original Erice Declaration of 1997 was a visionary statement of the achievable ideals for drug safety communication at the time, much of which remains potent and relevant today. Since then, however, the landscape has changed:

- ❖ Pharmacovigilance now extends to broader concerns relating to the safety of patients taking medicines, including medication error, off-label use, counterfeit products, erosion of trust and the potential risks to humans from drug residuals in the environment
- ❖ Dramatic information technology and electronic media developments worldwide have changed the nature of communications of all kinds
- ❖ The expansion and complexity of stakeholder involvement, and particularly societal and patient expectations, have radically altered the demands on healthcare providers and drug safety professionals.

New priorities and challenges have emerged as a result of the changes in these and other areas. Continued progress towards the ideals expressed in the original Erice Declaration is influenced - and sometimes hindered - by scientific and technical, but also political, financial, social and psychological factors.

- The authentic needs and wishes of the multiplicity of stakeholders, often with diverse and sometimes conflicting interests, are not well known.
- ◆ Active research must be undertaken to understand stakeholders' perceptions, requirements, roles and interactions
- ◆ Reciprocal partnerships must be built and managed based on mutual respect, sound knowledge, and with clear and agreed roles and responsibilities
- ◆ Targeted messages must be developed at a level of complexity matched to the abilities and needs of audiences, and using the richness of modern resources.
- There is extensive existing safety knowledge and experience outside the drug safety domain, and within it, that is not exploited and shared between individuals, disciplines and systems concerned with patient safety.
- ◆ Medicines safety communications with patients and the general public must be focused on achieving a culture of dialogue and joint-responsibility for safe and rational therapy
- ◆ Recognized health authorities must provide guidance for all audiences on finding, interpreting and assessing the reliability of safety information from existing sources, including unregulated information on the internet
- ◆ Existing knowledge and experience in drug safety communication must be given a much higher priority in all areas of professional education and training.
- Decisions in relation to drug regulation and therapy involve probabilistic assessments of risks and benefits, often based on limited information. Fear of litigation hampers open debate and transparency over judgements behind decisions, and clarity of information can be compromised by legal and legalistic concerns.
- ◆ A positive safety culture must be established, based on team-working processes and thinking that acknowledge responsibility, are free from blame and allocate accountability.
- The presence of widely dispersed drugs and drug metabolites in the environment poses a potential direct, and indirect, risk to humans.
- ◆ The nature and extent of the potential risks must be further investigated and assessed
- ◆ Safe disposal of medicines must be promoted, and appropriate facilities set up and used
- ◆ Further measures may have to be taken to reduce drug discharge into the environment, including education
- ◆ The promotion of rational drug use should reduce the volume of medicines finding their way into the environment.
- Progress in the area of gathering and storing health information brings with it challenges in ethics, and in assessing

and managing quality, of both the data and the systems.

- ◆ Active efforts must be made to promote and seek public approval of the use of anonymized patient information as essential for research and safe and effective therapy
- ◆ Those responsible for IT systems must ensure the highest level of security and quality to achieve public trust and willingness to contribute anonymized personal information.
- The media and professional communicators have an important role, not only as safety partners, but also in scrutinising the performance of drug safety systems.
- ◆ New ways to cooperate with the media as professional equals must be explored to help in the provision of balanced, comprehensible, trustworthy and interesting safety information to the public on a regular basis, apart from specific announcements or reports of problems or crises.

The participants were:

P.Bahri, UK
 M.Bassi, Italy
 A.Bourke, UK
 A.Castot, France
 A. Czarnecki, UK
 D. Darko, Ghana
 G. Deray, France
 A. Dodoo, Ghana
 B. D. Edwards, UK
 I. R. Edwards, Sweden
 B. Hugman, Thailand
 H. Lelouet, France
 M. Lindquist, Sweden
 N. Moore, France
 U. Moretti, Italy
 D. Muzard, France
 J. M. Ritter, UK
 P. Rizzini, Italy
 D. Szafir, France
 T. Trenque, France
 F.Turone, Italy
 K.Van Grootheest, the Netherlands
 G.P.Velo, Italy
 M. Vergnano, Italy.

The interests of all participants were openly declared.

continued on page 21

Worldwide ADR reporting patterns

Lars Melskens and Paw Petersen



Lars Melskens and Paw Petersen from Copenhagen, at the UMC in mid March

As part of our Master thesis project as graduate students at the Faculty of Pharmaceutical Sciences of the University of Copenhagen, we contacted the UMC in the autumn of 2009 with a proposal for a research project involving ADR reporting patterns for developing and developed countries. Shortly after, a collaboration was agreed to run for an 8-month period starting in January 2010.

ADR reporting patterns

The purpose of the project is to provide a general overview of reporting patterns for ADRs on a worldwide basis. The project will throw light on ADR reporting patterns across different income groups according to the World Bank's definition for developing and developed countries and also across different continents and regions.

parameters that will be analysed for the different countries and regions are as follows: type of report, type of reporter, type of therapeutic groups involved according to ATC classification, type of ADRs according to MedDRA System Organ Classes, the seriousness of the ADRs, gender and age of the patients, and distribution of ADR reporting over time.

Application of research

Few articles have been published on ADR reporting patterns – particularly for developing countries there seems to be a lack of information. We hope therefore that our project can contribute to knowledge of ADR reporting patterns that can be useful, especially for developing countries where the resources for pharmacovigilance often are very limited. Additionally, we hope that

our project will be useful for the WHO, national regulatory authorities in developed countries, the academia, drug manufacturers, and others with interest in pharmacovigilance, and help to strengthen the science of pharmacovigilance overall.

Acknowledgements

We are most grateful to both our internal advisor, Lise Aagard, associate professor at the Faculty of Pharmaceutical Sciences at the University of Copenhagen and our external advisor, Johanna Strandell, Drug Safety Analyst at the Research Department at the UMC for providing us with expertise and support for this project. We would also like to thank Professor Ebba Holme Hansen from the Faculty of Pharmaceutical Sciences at the University of Copenhagen for coming up with the original idea for the research project and the UMC for giving us the opportunity to work on this project and for extracting the data for us.

Future plans

We plan to finish writing up the project in August this year and an abstract will be available upon request from the UMC or the authors from September this year. Furthermore, we are aiming for the project to end up in one or more published scientific articles, and hopefully participation in international conferences.

Visitor from Japan

In February the UMC had a visit from Mr Hiroki Takuma. He is a pharmacist and PhD candidate at Professor Kiichiro Tsutani's laboratory at the University of Tokyo, Japan. Mr Takuma stayed for one week in Uppsala and worked with his research plan to develop a conversion table of Japanese Kampo formula in the WHO Herbal Dictionary. His study is supported by the Scientific Research Fund for Young Researchers of the Japan Society for the Promotion of Science.



Hiroki Takuma and Mohamed Farah discussing herbals at the UMC

Reactions Weekly editor

Jeanette Johansson

On February 15th, Rachel McLeay, Editorial Manager at Wolters Kluwer Health visited the Uppsala Monitoring Centre. Wolters Kluwer Health is a leading provider of information for professionals and students in medicine, nursing, allied health, pharmacy and the pharmaceutical industry. One of their brands is Adis, producer of peer-reviewed journals, decision-making tools and customized medical communications solutions.

Data for publication

Adis expert scientific editors collect the latest news from around 6,000 different sources including biomedical publications, relevant Medline and Embase indexed journals, major scientific meetings, newsletters from national centres participating in the WHO International Drug Monitoring Programme, media releases and regulatory agency websites. Senior specialist editors select the most important

items, covering labelling changes, drug withdrawals due to safety issues, safety updates from national centres, pharmacovigilance issues of current interest, treatment guidelines and adverse reaction research. Published adverse reaction case reports are gathered in the newsletter Reactions Weekly. Information is provided for therapeutic and prophylactic drug products, vaccines, monoclonal antibodies, recombinant proteins, herbal medicines and plasma products. Claims of 'first reports' are verified by a database literature search. For each adverse reaction case report verified as a first report, the Uppsala Monitoring Centre provides contextual adverse event data from the WHO Global Individual Case Safety Report (ICSR) database, VigiBase™.

UMC collaboration

The UMC is involved in several services related to the journal Reactions Weekly and one purpose for Rachel's visit was to discuss details in the contract between UMC and Adis. The other goal was to learn more about VigiBase and the search tool VigiSearch. During the afternoon Rachel got hands-on training in performing searches in VigiBase. The aim is that in the near future Rachel's editorial team at Adis will be able to perform their own searches in VigiBase.



Jeanette Johansson, Rachel McLeay and Cecilia Biriell

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The meeting was organized by the International School of Pharmacology at the Ettore Majorana Foundation and Centre for Scientific Culture in Erice, Sicily, Italy, in collaboration with the International Society of Pharmacovigilance (ISoP), SK Foundation and the Uppsala Monitoring Centre (UMC).

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New books

Global Pharmacovigilance Laws & Regulations: The Essential Reference

edited by Stephen L. Klinecicz, Yuung Yuung Yap and Adrian Thomas, with Jami L. Taylor

Soft cover, 300 pages;
ISBN: 978-1-935065-08-1



This book, published in April 2009 by the Food and Drug Law Institute, looks at the pharmacovigilance systems of over a dozen countries, analyzing the current state of pharmacovigilance from the viewpoint of practicing lawyers. The guide is organized according to the unique aspects of each country's legal system and regulatory structure, as an essential reference guide for lawyers, pharmacovigilance specialists, health officials, consultants and others in post-marketing surveillance. Despite increasing harmonization in regulation and pharmacovigilance, legal requirements continue to diverge, resulting in significant differences in medicinal product safety.

(see <http://www.fdpi.org/pubs/>)

Benefit-Risk Appraisal of Medicines: A systematic approach to decision-making

by Filip Mussen, Sam Salek, Stuart Walker
Hardcover, 304 pages

ISBN: 978-0-470-06085-8

Published in August 2009, this book describes a new tool for assessing benefits and risks for new medicines in development, aiming for transparent and responsible benefit-risk decision-making. This model employs a multi-criteria decision analysis involving the selection, scoring and weighting of key benefit and risk attributes.

The book considers the background and criteria required to assess benefit and risk in general, and looks at current practice by regulatory authorities and industry, and presently available models. Divided into the

following sections: Concept and Scope of Benefit-Risk, Criteria for a Benefit-Risk Model: a Conceptual Framework, Review of the Current Benefit-Risk Assessment Models, Defining a Systematic Approach to Decision Making and Development and Application of a Benefit-Risk Assessment Model based on Multi-Criteria Decision Analysis, there are appendices covering reports and papers.

Pharmacy practice in Spanish

Co-ordinated by Mariano Madurga of the Spanish Medical Products Agency, pharmacy professionals in Spain and Argentina recently made a Spanish translation of the WHO/FIP publication Developing Pharmacy Practice. A pdf is available for download at the website of FIP: http://www.fip.org/www/index.php?page=good_pharmacy_practice

New web-based education package

Kenneth Hartigan - Go

The first version of a detailed web-based training project is being launched. The intention is to provide medicine safety education reach across a number of stakeholders (academe, government, hospitals, households, media, schools, and workplaces) so they can become familiar with the subject or use the materials to teach basic medicine safety. There are also references and a sound commentary to use while in the programme, which is accessible at <http://idhphil.com/pharmacovigilance/> The original project was made possible through a grant from the World Health Organization.

UMC on the radio

Marie Lindquist, UMC Director, was on Swedish radio in February, being interviewed about the safety aspects of swine flu vaccination in Sweden. The programme 'World of Knowledge', on national Swedish radio, is broadcast every week, and Marie was able to talk generally about the importance of pharmacovigilance. A link to the 20-minute interview (in Swedish) is here:

<http://sverigesradio.se/sida/gruppsida.aspx?programid=406&grupp=7641&artikel=3433595>

2010 release of WHO-ART

Cecilia Biriell

The 2010 version of WHO-ART has recently been released to customers. From this year WHO-ART will only be released once a year, but the internal UMC database is still updated continuously as needed.

Updated translations

UMC has received valuable help from some national pharmacovigilance centres to translate WHO-ART into the most frequently used languages. The translation into Portuguese which has not been updated for some years is now complete. The French and the Spanish versions have recently been updated and are now up to date.

MedDRA bridge

Since many users of WHO-ART have to report to other organizations in MedDRA terminology a bridge on the Preferred term level was implemented two years ago. This bridge is now updated to the 2010 WHO-ART and 13.0 MedDRA versions. UMC still accepts ICSRs in both WHO-ART and MedDRA terminology.

The updated files of WHO-ART, including all available languages, and including the WHO-ART - MedDRA bridge, are available to commercial customers from the UMC Products & Services department (sales@umc-products.com). The files are distributed free of charge to National pharmacovigilance centres in the WHO programme not using VigiFlow, where WHO-ART is included in the software, or MedDRA.

No updated versions of WHO-ART in printed format have been produced this year.

DATES	TITLE	PLACE	ORGANISER/CONTACT
5 May 2010	Introduction to Signal Detection and Data Mining	Horsham, PA, USA	DIA Phone: +1-215-442-6158 E-mail: Ellen.Diegel@diahome.org
6-7 May 2010	Latest developments in pharmacovigilance (advanced course for experienced personnel)	London, UK	Management Forum Ltd www.management-forum.co.uk Tel: +44 (0)1483 730008 E-mail: registrations@management-forum.co.uk
12-13 May 2010	Keeping up with the constantly-changing regulatory environment for pharmacovigilance	London, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
27-28 May 2010	Basic pharmacovigilance course & Clinical trial safety course	Belgrade, Serbia	International Society of Pharmacovigilance www.isoponline.org/training.html
2-4 June 2010	Practical Guide for Pharmacovigilance: Clinical Trials and Post Marketing	Prague, Czech Republic	DIA Europe Tel: +41 61 225 51 51 Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org
21-23 June 2010	Pharmacovigilance : a basic course for those working on safety monitoring in the EU, USA and Japan	London, UK	Management Forum Ltd www.management-forum.co.uk Tel: +44 (0)1483 730008 E-mail: registrations@management-forum.co.uk
30 June - 2 July 2010	Medical Aspects of Adverse Drug Reactions	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
19-22 August 2010	26th ICPE	Brighton, UK	ISPE www.pharmacoepi.org/meetings/ E-mail: ISPE@paimgmt.com
8-9 September 2010	Back to Basics in Pharmacovigilance	Botley, Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
13-14 September 2010	Medical Approach in Diagnosis and Management of ADRs	Paris, France	DIA Europe Tel: +41 61 225 51 51 Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org
20-22 September 2010	Drug Safety Surveillance and Epidemiology	Horsham, PA, USA	DIA Phone: +1-215-442-6158 E-mail: Ellen.Diegel@diahome.org
22-23 September 2010	Critical Appraisal of Medical and Scientific Papers: How to read between the lines	Fareham, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
30 September- 1 October 2010	X Jornadas de Farmacovigilancia	Valladolid Spain	Spanish Medicines Agency / Regional Health Authority of Castilla-y León www.farmacovigilancia2010.es
20-21 October 2010	Risk Benefit Assessment in Pharmacovigilance	Botley, Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org ; www.dsru.org/
25-29 October 2010	Excellence in Pharmacovigilance: Clinical Trials and Post Marketing	Vienna, Austria	DIA Europe Tel: +41 61 225 51 51 Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org
29-31 October 2010	5th Asian Conference on Pharmacoepidemiology Introduction to Signal Detection and Data Mining	Tokyo, Japan	ISPE www.pharmacoepi.org/meetings/ E-mail: ISPE@paimgmt.com
3 November 2010	Introduction to Signal Detection and Data Mining	Horsham, PA, USA	DIA Phone: +1-215-442-6158 E-mail: Ellen.Diegel@diahome.org
3-6 November 2010	10th ISoP Annual Meeting: 'Pharmacovigilance in the Global Village'	Accra, Ghana	International Society of Pharmacovigilance www.isop2010.org
8-11 November 2010 14-17 February 2011 11-14 April 2011	Certificate in Pharmacoepidemiology & Pharmacovigilance	London, UK and distance learning	London School of Hygiene and Tropical Medicine Tel: +44 (0)20 7299 4648 E-mail: shortcourses@lshtm.ac.uk; www.lshtm.ac.uk/prospectus/short/scpp.html



The Uppsala Monitoring Centre (*the UMC*) is the field-name of the WHO Collaborating Centre for International Drug Monitoring, responsible for the management of the WHO Programme for International Drug Monitoring.

An independent centre of scientific excellence, *the UMC* offers products and services, derived from the WHO global ICSR database, VigiBase™ reported from member countries of the WHO Programme.

With an independent and global perspective on drug safety, *the UMC* provides resources for regulatory agencies, health professionals, researchers and the pharmaceutical industry.

The UMC's important worldwide work is financed solely by the organisation itself, without support from WHO, the Swedish Government, member countries of the WHO Programme or any grant-making body.

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