

# UUR 41

**UPPSALA REPORTS April 2008**

For everyone concerned with the issues of pharmacovigilance

**New directions in pharmacovigilance**

**October 2008 - a major week in Uppsala**

**A fresh start in Italy**

**MedDRA in the WHO ADR database**

**Visitors at the new UMC office**



# DIRECTOR'S MESSAGE



Ralph Edwards  
Director  
the Uppsala Monitoring  
Centre

Perhaps promoted by the controversy over Vioxx, and two reports on the future of pharmacovigilance, one in the USA and the other in the EU, there is now a kind of 'feeding frenzy'. Many new organisations and people are chasing resources that have become suddenly available. After 40 years the WHO Programme for International Drug Monitoring, and the UMC, have become fashionable again and people are contacting us seeking information and partnerships for global and local initiatives. Sounds good?

Well possibly! For a group that has been fighting for resources for half a lifetime, whilst doing the best it can, and with many successes, feelings can be mixed. Should it really take a major drug withdrawal to bring the topic of drug-related morbidity and mortality to the fore? It seems as if nobody has been interested in the morbidity and mortality statistics we and others in pharmacovigilance have presented over years: they clearly show the importance of drug-related injury to individuals and to public health, with the associated costs to society. This may well be our collective deficiency in communication, but we have had the limitation of resources for that task as well. Many people now want to talk to us about pharmacovigilance, without knowing any of those background achievements and problems we have faced, and explanations can be very time consuming!

Groups outside the current pharmacovigilance community are seeking and getting money for 'new' ideas, but many of those 'new ideas' can often be found by searching the literature from the 1960s and 70s. We have also been trying to develop those ideas over the years: there has been no shortage of good ideas, only resources. This interest in new approaches is understandable in one way because our continuing use of the cheapest globally useful method for safety monitoring 'spontaneous reporting' is regarded as a 'failure': we 'missed' the Vioxx problem. But I must remind sceptics yet again that the signal on Vioxx and myocardial infarction was found using ICSR (individual case safety report) data, and prominently reported by the Netherlands centre (Lareb) at a WHO National Centres Meeting (Tunis, October, 2000) only 6 months after the launch of Vioxx. In my view, any reason for 'failures' over Vioxx, or most other product withdrawals, has always been lack of resources in following up signals.

The current interest in finding signals in clinical trials is problematic both because of their often low population coverage or the cost of large enough studies. Observational studies have their limitations for finding signals also, as does cohort event monitoring. The main drawback of all these approaches is that they are limited to a few drugs for limited periods of use. The only 'catch-all' alternative approach to 'spontaneous reporting' to find drug-related event signals seems to be some knowledge-finding tool used on large health care databases. We are investigating and using such an approach, but much needs to be done to be sure that it is an alternative (rather than a supplement) to 'spontaneous reporting'. I believe we still have some way to go before we use our existing tools optimally and in conjunction, rather than trying to find a single 'best' tool. After all, we use both hammers and screwdrivers without trying to decide which is best overall!

We very much welcome new interest and ideas into pharmacovigilance, but I would also make a plea for anyone newly interested in global pharmacovigilance to do their homework, and not to ignore the successes, the systems, and the knowledge and wisdom, that exist in the WHO Programme and elsewhere. Moreover, I would promote the concept of true co-operation: we will work with anyone who reasonably shares their resources and ideas with us for the furtherance of patient health and the reduction of the public health burden of iatrogenic disease. What is annoying is competition for funds for re-inventing the wheel, rather than building on what already exists, and often works well. Even where it does not work well enough is no reason to necessarily start from the beginning.

We too, are innovative and are continuously developing ways of doing things and partnerships for doing them, but building on what is already there and not unnecessarily competing with others. In our work we are always trying to ensure that best possible science and professionalism are benefiting poor as well as the rich. We will continue to pursue the ideal of trying to equalise the standards of patient safety across the globe, but always upwards to the best standards for everybody, not downwards: please help us reach this goal.

In summary, let's not re-invent pharmacovigilance wheels, but add pneumatic tyres for a safer, smoother ride into the future!

A handwritten signature in black ink, reading 'Ralph Edwards', written in a cursive style.

2	Director's Message
	News from Around the World
4	WHO Programme news
5	Annual Meeting in Uppsala
6-7	USA, Andorra, Tanzania
8-9	Developments in drug safety
11	Vaccine safety news
12-13	Focus on Italy
14	MedDRA in Vigibase
15	Drug Dictionary update
16-17	Reports from Buenos Aires, Bangkok, Geneva
18-19	News from <i>the UMC</i>
20-21	Visitors to <i>the UMC</i>
21-22	Publications news
23	Courses and conferences
24	<i>the UMC</i> team



## 5 Annual Meeting and more...

A major 'open' research meeting and other WHO meetings are grouped around the 31st Annual Meeting of the WHO Programme in Uppsala this October.



## 10 Patient Safety

2nd meeting of international medication error group in Dublin.



## 8, 11, 17 Drug Safety at WHO HQ

Reports from several recent meetings concerning drug safety held at the HQ of WHO in Geneva.



## 17 From strength to strength

Bangkok hosts two highly successful ISoP training courses.



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 database of Adverse Drug Reactions (ADRs) 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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## Togo joins the Programme



Edinam Agbenu

Following a workshop on pharmacovigilance in Togo in December 2006, then participation in the pharmacovigilance training course for African Francophone countries in Rabat, Morocco in February 2007, Togo, along with several other west African countries, became an Associate member of the WHO Programme in May 2007. Edinam Agbenu then attended the WHO training of consultants in pharmacovigilance meeting in July 2007 in Accra, Ghana. Strengthened

by these capacity building courses and the involvement of the main public health programmes – HIV, malaria, TB, immunization – Togo has moved to become a full member of the WHO Programme in January 2008.

The existence of a pharmacovigilance programme is gradually becoming better known in the country. A room in one teaching hospital has been allocated for pharmacovigilance activities, and a plan for extension has been made, together with anti-retroviral (ARV) dispensing so that it can help reduce discrimination for people coming for their ARVs. They are hoping to provide general public drug information, and ADR monitoring to a specific population in ARV dispensation.

Over 500 ADR notifications are registered. Two surveys are being conducted, one in hospitalized patients and the other in pharmacy shops. All the public health programmes are joining the pharmacovigilance system to ensure ADR monitoring to their targets. In the next year or two, the plan is to implement activity in the districts, conduct more surveys and train more professionals on notification and causality assessment.

In late March the Ministry of Health of Togo signed the act to formally recognize the pharmacovigilance system, giving it a legal status to move forward. The question of funding of pharmacovigilance in the health budget will also soon start in earnest.



The pharmacovigilance centre beside the drug store of the hospital.

In November a workshop to design a programme to train public health pharmacists took place at the Regional Institute of Public Health (IRSP in Ouidah, Benin). "Pharmacovigilance has found its place in the programme and will join with medical doctors whose programme exists already" writes Edinam. The plan

for a network for African countries will be more developed at the Forum of Pharmacists in Libreville. The intention is for countries to help one the other in setting up a strong pharmacovigilance system in Africa. Medical doctors would monitor ADRs systematically when prescribing, and pharmacists in 'officines' (pharmacy shops) would be more active, since all patients go there with or without a prescription.



Pictured on the wall poster:

One man informing his neighbour that the one in the middle reacted to a drug and they would stop the medicines. His neighbour (right) answering that he should first contact his doctor or the pharmacist and not forget to notify the centre for pharmacovigilance.

The current contact details are:

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Direction des Pharmacies Laboratoires et Equipements Techniques  
Ministry of Health  
BP 336 Lomé Togo  
Tel: +228 9462177  
elhaidnam@hotmail.com

### New Associate Member

Montenegro (Crna Gora) has applied to become a member of the WHO Programme.

A letter has been sent by Dr Miodrag Radunovi, Minister of Health in Podgorica, to Dr Mary Couper at the WHO in Geneva, notifying her of their wish to join the Programme, with Ms Maja Kovacevic as the contact person. This follows re-structuring of drug and other medical supplies organisation in Montenegro.

# Come to Uppsala in October

There will be something for everyone this October when the 31<sup>st</sup> Annual Meeting of countries participating in the WHO Programme for International Drug Monitoring takes place in Uppsala. Hosted by the Uppsala Monitoring Centre and the Swedish Medical Products Agency, it will take place on Monday to Thursday 20-23 October.

For new delegates and countries which have never attended the annual meeting there is an afternoon seminar to give basic background information on the way the Programme works.

We very much hope that delegates from national centres will stay on in Uppsala after the Annual Meeting for an open research meeting on 24 October with some distinguished speakers. This research meeting will showcase the latest methodology and findings in ADR signal detection, and point out important directions for future research. It will be of great interest to all working in pharmacovigilance, particularly in the area of signal detection. A top-level group of chairpersons and panel members will provide a review of state-of-the-art quantitative and qualitative signal detection in spontaneous reports and other healthcare datasets. The registration form is now accessible via *the UMC website*.



In addition, those interested in learning how to apply ATC classification of medicines and Defined Daily Doses (DDDs) may attend a specific training day on 24 October, organized by the WHO Collaborating Centre for Drug Statistics Methodology, Oslo. A selected group of representatives at immunization centres focusing on vaccine safety will be invited separately for a meeting 17-18 October.

So we urge all national centres to plan to make full use of these educational and networking opportunities in Uppsala!

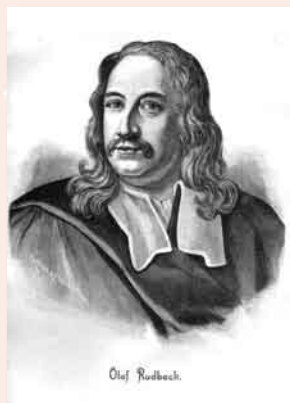
*the UMC* has reserved rooms in hotels around the city and is putting the finishing touches to an exciting social programme.

We look forward to seeing many of you in Uppsala in six months time!

The full schedule of meetings to coincide with the WHO Annual Meeting is:

17-18 October	WHO Vaccines Safety meeting
19 October	WHO Programme 'new delegates/countries' seminar
20-23 October	31 <sup>st</sup> WHO Annual Meeting
24 October	Impacting patient safety: Adverse drug reaction signal detection - <b>Booking now open</b>
24 October	Training course on DDD/ATC methodology
25-26 October	UMC Signal Reviewers

## Uppsala – A glorious scientific history



Olof Rudbeck (1630-1702) made what has been called 'the first scientific discovery by a Swede', the lymphatic gland and its diffusion in the human body. He had a botanical garden established, set up boat connections with Stockholm, built bridges and aqueducts and constructed the Anatomical Theatre in the Gustavianum – as well as being a composer who sometimes performed in the cathedral.

Carolus Linnæus (Carl von Linné) (1707-1778) wrote *Systema Naturæ*, which laid the foundation of a new way of categorizing plants, based on their reproductive systems, replacing earlier impractical and complicated systems. In 1741 he had a chair at the Faculty of Medicine at Uppsala, and undertook research journeys within Sweden from which his travel notes are an invaluable resource.

Anders Celsius (1701-1744) published observations regarding "two constant degrees on a thermometer". His system was based on the zero point marking the boiling point of water, and 100 degrees when snow melts. These points were later reversed, but Celsius's thermometer prevailed and is now used for scientific measurement.

The chemist Torbern Bergman (1735-1784) did pioneering work in analytical chemistry in a laboratory off Västra Ågatan, and created the concept of 'elective affinities'. In the 1770s Bergman collaborated with Carl Wilhelm Scheele (1742-1786), who worked as an apothecary and was behind the discovery of oxygen.

The father of separation chemistry, The Svedberg, professor at Uppsala University, was awarded the Nobel Prize for Chemistry in 1926. His ultracentrifuge made it possible to separate, characterize, and determine the weight of proteins. One of Svedberg's students, Arne Tiselius (Nobel Prize in 1948) invented a new method for the separation of molecules and particles, electrophoresis, used today to read the text of genes.

In 1960 Leif Wide developed the first simple pregnancy test in history.

Uppsala scientists can also claim credit for advances in ophthalmology, including Healon, a hyaluronic acid preparation used in cataract operations. Eye research was established by Allvar Gullstrand (1911 Nobel Prize for Medicine).

## Gazing into the future at the US FDA

'Maximizing the public health benefit of adverse event collection throughout the product life cycle'

Ralph Edwards

A one-day public workshop on the future of pharmacovigilance was organised by the US FDA in Washington on 29<sup>th</sup> January. More specifically three FDA presenters skilfully led the debate into a discussion about the future of the value of ICSRs (individual case safety reports), given that analysis of longitudinal health care data now had practical potential in detecting drug-related adverse events.

For some years, I have urged WHO Programme members to evaluate what impact their work has on public and individual healthcare. Our self and peer evaluations have been limited, sporadic and primitive. For the most part we have been limited to pointing to the numbers of drug withdrawals (without much assessment of justification) and changes to SPCs. This meeting signalled the FDA's determination to change that.

### Evaluation – the position so far

The FDA staff treated us to a historical overview of the developments in drug safety in the FDA, and to the current practice. The presentations were detailed critical evaluations. They also gave us a tantalizing preview of what they had in mind for their evaluation of spontaneous reporting by showing that, for new drugs registered between 1991 and 2006, drug safety issues were identified in the AERS (the FDA spontaneous report) database throughout the product's life in that period which required some regulatory action. This simple result starts to answer some basic but important questions such as, "How long do we need to monitor a product?" Some other issues that were identified for investigation were the need to talk to individuals involved in review and decision-making on ICSR data, and the time sequence between signal discovery, analysis and regulatory action. The latter would be very interesting if it were to review what signals were discarded, and why.

Most important, the presentations jump-started the first scheduled discussion of the day, and the task in hand was identified: 'As we begin to transform and modernise the science of drug safety, this is the time to stop and scientifically evaluate the public health impact of spontaneous AE reporting'. How right and how explicit!

### ICSRs – the why and wherefore

The FDA had brought the first panel to Washington to debate what questions should be asked and answered by the AERS database, what was its current value, and what could be done in the future. The panellists included prominent experts from other US federal agencies, the pharmaceutical industry, medical and pharmacy professionals, patient advocates, academia and international representatives.

As expected, the usual problems and drawbacks with ICSRs were mentioned, but there was no disagreement with the need for

continued reporting by health professionals and consumers. The reasons given included reporting as a two-way communication between regulators and their public – to have a way for them to express concerns about medications and therapy, and to feel part of a network; to obtain qualitative information on harms from medicines; to take early advantage of original observations of health professionals and consumers on possible ADRs; in general to have an economical system which covers all medications including OTCs, and to cover varying safety situations such as misuse of medicines and counterfeit drugs. The paramount issue of considering patients' safety rather than 'drug safety' was mentioned a few times. In respect of this point it seemed clear that consumer reports had the potential to identify therapeutic errors that might not be otherwise reported.

### Methods and objectives

The second panel had the same broad expertise as the first, with some overlapping membership. The task was to identify the best methodologies to use in researching the value of the AERS dataset.

Perhaps not surprisingly some of the same ground was covered as in the first panel, and there were strong views expressed as to the value of moving towards the analysis of longitudinal patient records. There was no disagreement regarding the need to move in that direction, but most believed that ICSR data would have continuing utility. There was strong endorsement of the general way in which the FDA was approaching the challenge, based on the introductory presentations. There was general agreement that the main end points should be identifiable public health benefits. Views were expressed over groups and resources that may be brought to bear on aspects of analysis, but no precise proposals were made. It was very clear that much good will existed in supporting this endeavour by the panellists and other participants.

All in all, this was a very useful meeting, setting the stage for key work to be done in evaluating pharmacovigilance performance in the USA, and with global significance. My brief overview I am sure contains some of my biases, and there are many omissions of important insights presented. For those interested in more information go to <http://www.fda.gov/ohrms/dockets/meetings/cmmeetings.htm>, where you will find the background information to the meeting, and where a transcript of the meeting is promised.



## Official launch in Andorra

Cristina Vilanova Serrano from the Pharmacovigilance Unit at the Ministry of Health, Welfare, Family and Housing in Andorra reports that an inaugural session of the safety programme in her country took place on 28<sup>th</sup> January.

A presentation of the pharmacovigilance program to health care workers (pharmacists, physicians and nurses) took place. The Ministry of Health gave an introduction after which Cristina explained how the program worked. Professor Joan-Ramon Laporte, director of the Fundació Institut Català de Farmacologia in Spain gave an interesting talk about adverse drug reactions and their impact on public health which was much appreciated by the audience. The following day the Andorran media gave the event wide coverage.



Left to right: Joan-Ramon Laporte, Montserrat Gil (Minister of Health, Welfare, Family and Housing), and Cristina Vilanova Serrano

## CEM of ACTs being planned in Tanzania

Stimulated by an initiative from the RaPID consortium (see UR38, p6) and supported by the Roll Back Malaria Partnership, the Tanzania Food and Drug Agency (TFDA) is working together with the National Malaria Control Programme (NMCP) in designing a Cohort Event Monitoring (CEM) study of artemether – lumefantrine. This medicine combination was recently recommended as the first line treatment of malaria in Tanzania.

Paul Lalvani of the RaPID initiative invited Dr David Coulter, a CEM expert from New Zealand and Sten Olsson of *the UMC*, to a meeting on 15–16 March 2008 in Dar es Salaam. With representatives of the two agencies and other supporting organizations, the study protocol was discussed in all its practical details. It is an adaptation of the Manual for Pharmacovigilance of Anti-Malaria Medicines which is currently being published by WHO. At the meeting it was concluded that 10,000 patients treated with artemether – lumefantrine should be followed up one week after initiation of treatment for recording of possible adverse events. Having decided on the sentinel sites from which patients would be recruited, it was estimated that data collection would take around one year.

The Department of Medicines Policy and Standards of WHO is supporting the study with start-up funding but further sources for financial support to fully accomplish the study are now being sought from various funding agencies.

## Global pharmacovigilance survey

As mentioned in UR40, WHO has entered into a joint project with the University of Washington, Seattle, USA, for the development of a Global Pharmacovigilance Strategy. The first part of the project is to document and describe present pharmacovigilance activities in the world. *the UMC* was commissioned to carry out the investigation that relates to pharmacovigilance activities carried out by official institutions in the public sector with a focus on countries outside of the ICH area (ie, excluding North America, European Union and Japan). A detailed questionnaire designed by *the UMC* in close collaboration with the project managers was made available in English, French and Spanish, and distributed mid-March to contact persons in over 100 countries. The English version was also made available on-line on *the UMC* web site.

The project managers organized a meeting of key stakeholders in Amsterdam on 8–9 April 2008, at which the interim results of the country pharmacovigilance investigation were presented. Almost 50 of the country contact persons had provided answers in time for the meeting. A good basis for identification of current needs in pharmacovigilance development was available and discussions were held on how best to meet them. The objective of the current project is to submit a full proposal for funding of global pharmacovigilance activities to the Bill and Melinda Gates Foundation later this year.

At *the UMC* we will continue our efforts in documenting the pharmacovigilance situation in non-ICH countries. We will follow-up with countries that have not responded to our inquiry. The more comprehensive information we have, the better we will be able to address needs specific to certain regions or types of countries. We wish to extend our sincere thanks to all those who quickly responded to our call and spent time to complete the rather extensive questionnaire.

## ARV drugs adverse events definitions

The WHO Departments of HIV and Medicines Policy and Standards together with the Forum for Collaborative HIV Research, and with the support of the Bill and Melinda Gates Foundation, organized a meeting in Geneva on 28-29 February 2008. The meeting was attended by 65 experts in pharmacovigilance, clinical HIV medicine and laboratory science, with representatives from governments, academia, international pharmacovigilance networks, pharmaceutical companies, and non-governmental organizations. Marie Lindquist attended on behalf of *the UMC*.

### Common language needed

The objective in bringing together the pharmacovigilance and HIV treatment communities was to establish a common language to harmonize adverse event case definitions, and hence the detection, recording, reporting and analysis of adverse event data related to the use of antiretroviral drugs (ARVs). The ultimate goal is to develop a thesaurus of definitions of these adverse events of ARVs and contribute to improving global pharmacovigilance for antiretroviral drugs, with particular focus on resource-limited settings, children and special populations.

The meeting resulted in the generation of a list of major adverse events for surveillance related to the use of antiretroviral drugs.

### Consensus on terms

Consensus was reached on the need to make available terms and definitions for adverse events that are applicable at all levels of health care. Meeting participants endorsed a process for the development of a priority list of specific case definitions by expert panels that can be used in treatment settings. In addition, it was recommended that expert panels develop severity grading of adverse events based on clinical and laboratory findings, as needed.

Participants agreed on the principle of establishing sentinel surveillance sites for active reporting of adverse events in all countries including countries where pharmacovigilance systems for antiretroviral drugs still need to be developed. These sentinel sites will be linked to both national and international networks and need to be representative of the different levels of the health care system.

In addition, spontaneous reporting should be further strengthened in countries where pharmacovigilance systems have already been established, and where training and feedback is sustained. Known and unexpected adverse events will continue to be captured through existing passive pharmacovigilance reporting.

### Remaining issues

On severity grading there were more questions than answers:

- which grades to be used? (mild, moderate, severe, life-threatening)?
- should only serious events be reported?
- should a severity threshold be defined to enable comparability?

Expert panels will be convened to decide which qualified adverse events linked to antiretroviral therapy apply to specific population subgroups and to make toxicity grading recommendations.

### Next steps

The review of the listing of terms and definitions (priority and extended lists) will be carried out in small working groups based around the System Organ Class (SOC) classification of WHO-ART. These expert teams identified by WHO HIV and Procurement and Supply Management (PSM) Departments will include clinicians and pharmacovigilance experts.

Once this work is completed, the PSM and HIV Departments will convene a meeting of experts to establish a consensus on

- the final thesaurus document
- reporting forms, protocols and systems to report recorded adverse events linked to antiretroviral therapy
- coding, data compilation, analysis and management
- compliance with current international standards, and
- operational linkages with existing systems (MedDRA, WHO-ART), the cohort implementers and existing national PV programmes.



# IMPACT meet in Lisbon

An IMPACT (International Medical Products Anti-Counterfeiting Taskforce) General Meeting took place in Lisbon, Portugal on 12-13 December 2007, with 40 governments represented along with representatives of INTERPOL, the World Trade Organization, European Commission, Council of Europe, FIP (International Pharmaceutical Federation), Pharmaciens Sans Frontières, ReMeD, and associations representing pharmaceutical manufacturers and wholesalers. Presentations are available on IMPACT's web site ([www.who.int/impact](http://www.who.int/impact)).

## Legislative Infrastructure

A draft document 'Principles and Elements for National Legislation against Counterfeit Medical Products' was discussed at a separate meeting on 10 and 11 December, then endorsed in a plenary on 12 December 2007. The final version is available on IMPACT's website.

During 2008 IMPACT will encourage national/regional parliaments to debate legislation on counterfeit medical products on the basis of IMPACT's principles. This has been made possible by funding from the European Commission. One approach to be explored is for WHO to send a hard copy of the document to all Member States with an official request to provide feedback to improve the legal framework at national level. A comparative study of implementation of anti-counterfeiting legislation is being conducted by the Max Planck Institute, to report in 2008.

## Regulatory Implementation

A draft text proposing revisions to WHO's Good Distribution Practices was endorsed. IMPACT Secretariat has submitted it to the WHO's Expert Committee on Specifications for Pharmaceutical Preparations, and feedback is expected by June 2008.

## Enforcement

The meeting endorsed a 'Guide to Investigating Counterfeiting of Medical Products and other Pharmaceutical Crimes' developed by the Permanent Forum on International Pharmaceutical Crime. It is envisaged to finalize the text and print enough hard copies to conduct training of regulatory and enforcement officers.

## Communication

A revised Rapid Alert System allowing member states to report cases and receive alerts when new cases are reported will be developed for a global audience, based on the RAS developed by WHO's Western Pacific Regional Office.

## Internet Sales

EBay and the Portuguese Regulatory Agency (Infarmed) presented their experiences on the internet trade of medicines. Infarmed strategy encompasses both regulatory and communication aspects. A law of August 2007 allows medicines to be bought from internet pharmacies, but delivery takes place at the pharmacy and the patient shows the prescription at that point. No on-line (or any other) advertising of prescription medicines is allowed in Portugal. In addition, the Portuguese government has launched a campaign to raise awareness of the dangers of counterfeits purchased over the internet. EBay's representative explained the efforts the company makes to prevent the illegal sale of pharmaceuticals on their platform. There are clear policies on what type of products can and cannot be sold, and medicines are not allowed.

Noting that e-trade requires a multi-pronged approach it was decided that a single IMPACT document/guide addressing the advertisement/sale of medical products through the internet will be prepared with input sought from different working groups.

The date and place of the third General Meeting of the IMPACT has not yet been decided but is likely to take place outside Europe.

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# Second version of WHO-ART – MedDRA mapping released

In March last year the first version of the WHO-ART – MedDRA mapping was produced. The mapping has now been updated with changes in the two terminologies since then and is up to date with terms in WHO-ART first release 2008 (081) and MedDRA 11.0.

The mapping contains all WHO-ART preferred terms with a link to closest MedDRA terms which may be on either Low level or Preferred level, and also giving codes for both WHO-ART and MedDRA terms.

This mapping is 'one-sided' in that it links WHO-ART terms to MedDRA terms, but should not be used the other way around. The mapping is intended for WHO-ART users who may want to be able to present or send data in MedDRA terminology to others and is provided as a txt-file free of charge to all WHO-ART and MedDRA customers.

The implementation of MedDRA in Vigibase is different in that a mapping of all WHO-ART terms, both Included and Preferred terms, has been made to MedDRA terms and vice versa from all MedDRA terms that have been reported to Vigibase.

[See also article on page 14.](#)

## International medication error group formed

At the 30th annual meeting of representatives of national centres participating in the WHO Programme for International Drug Monitoring (10-13 October 2007) a working group highlighted the importance of identifying medication errors related to improper use of medical products<sup>1</sup>. In this regard, it was noted that existing roles of pharmacovigilance centres are expanding in monitoring medication errors. However, it was also recognized that a limitation of existing systems is that they are mostly not ready for root cause analysis and appropriate clinical response to corrective actions, especially in terms of speed.

### IMSN formed

Assistance with global regulatory efforts may be available to pharmacovigilance centres or may be forthcoming. In 2006, in Salamanca, Spain, a group of international physicians, pharmacists and nurses who work as patient safety experts and specialize in medication error prevention in their countries, met to form an organization to support international efforts in this regard. The group is known as the International Medication Safety Network (IMSN), an international network of safe medication practice centres. Their website [www.intmedsafe.net](http://www.intmedsafe.net) contains the group's charter.

### Purpose of IMSN

IMSN recognizes that harm from medication errors occurs in all countries and that much can be learned from the analysis of medication errors with the support of confidential, non-punitive and independent reporting and learning systems. Countries and organisations with these systems are better placed to protect patients, educate healthcare professionals and support institutions to prevent medication errors and implement safer medication practices. The group's charter calls for supporting safe medication practice centres and establishing medication error reporting systems to communicate safety issues to healthcare professionals and patients, and to advocate safe practices at all levels in the healthcare system.

The centres act as independent focal points (centres) for safe medication practice in a collaborative, complementary, yet distinct way from pharmacovigilance systems. The IMSN would welcome programmes for interaction with these centres in order to share information and expertise, offer assistance in evaluating medication errors and support for dissemination and implementation of medication-related patient safety solutions, especially those developed by the WHO World Alliance for Patient Safety.

### International collaboration

Informal interaction and collaboration has occurred in North America between the United States Food and Drug Administration (FDA) and the Institute for Safe Medication Practices (ISMP) and between Health Canada and the Institute for Safe Medication Practices Canada and in the UK between the National Patient Safety Agency (NPSA) and the Medicines and Healthcare Products Regulatory Agency (MHRA). Safe medication practice centres also exist in Spain

(ISMP Spain), Denmark and the Netherlands. Efforts are now underway to create similar operations in Australia, Brazil, Saudi Arabia and Singapore. Hong Kong has a government-supported effort through the Hong Kong Hospital Authority.

### Busy meeting in Dublin

A second international IMSN meeting took place in Dublin, Ireland in November 2007. Delegates attending represented Brazil, Canada, Denmark, France, Hong Kong, Ireland, Israel, the Netherlands, Saudi Arabia, Singapore, Spain, Sweden, the UK and the USA, while delegates from Australia and New Zealand participated via teleconference. Representatives from the WHO World Alliance for Patient Safety and Joint Commission International, which is leading WHO Patient Safety Solution efforts, also attended. The group identified and discussed a number of medication error related issues common across nations including drug name confusion between morphine and hydromorphone, insulin labelling, inadequate labelling



*Chairperson Michael Cohen (left) and ISMP Brazil representative Mário Borges Rosa at the Dublin IMSN meeting*

and packaging of certain products, errors with transdermal fentanyl, accidental intrathecal injection of vincristine, and many others. IMSN has prepared a global report, that will include qualitative and quantitative data about medication errors in member countries, and will be posted shortly on the group's website.

The timing seems right for improved global understanding about product-related user error. Support and co-operative improvement efforts must be applied proactively when approving products but also retroactively everywhere products are used. The IMSN is committed to working with global authorities to facilitate these efforts with the pharmaceutical industry and regulatory agencies in their respective countries. Despite language differences, the information contained in a product's name, package, and label is universal and must be clear for all pharmacists, physicians, nurses and patients worldwide who must make decisions based on the information presented.

Those interested in learning more about IMSN efforts or even participating in the group as a country delegate should contact the chair:

Dr Michael R Cohen  
Chairperson  
International Medication Safety Network  
c/o Institute for Safe Medication Practices  
200 Lakeside Drive  
Suite 200  
Horsham PA 19044 USA  
www.ismp.org  
e-mail: mcohen@ismp.org

1. Reference: WHO. Patient safety: extending the scope of pharmacovigilance centres. WHO Pharmaceuticals Newsletter No. 5, 2007

## Vaccine Safety News

### 17th Meeting of the Global Advisory Committee on Vaccine Safety.

The Global Advisory Committee on Vaccine Safety (GACVS), an expert clinical and scientific advisory body established in 1999 to respond, independently from WHO, promptly, efficiently, and with scientific rigour to vaccine safety issues of potential global importance, held its seventeenth meeting in Geneva, Switzerland, on 12–13 December 2007. Issues discussed were: Guillain-Barré syndrome and vaccination; the safety of immunization for immunocompromised individuals; yellow fever vaccine safety; hepatitis B vaccination and rheumatoid arthritis; the safety of the live 14-14-2 Japanese encephalitis vaccine; the safety of meningococcal B vaccines; and rotavirus vaccines and Kawasaki disease.

Information on several of the topics discussed follows.

#### Hepatitis B vaccination and rheumatoid arthritis

The Committee considered the potential association between hepatitis B vaccination and rheumatoid arthritis. Prior to previous discussions on this topic held in June 2006, the Committee had commissioned a comprehensive literature review. At this meeting, the Committee reviewed more recent information, particularly on genetic issues.

The Committee concluded, based on review of the limited data available, that there was no convincing evidence to support an association between hepatitis B vaccination and rheumatoid arthritis. The topic will be considered further if new findings become available.

#### Safety of meningococcal B vaccines

The Committee was presented with safety data relating to use of outer membrane vesicle-based meningococcal B vaccines in Cuba, France, New Zealand and Norway.

The Committee noted that several new meningococcal vaccines were being developed, at least one of which is closely related to the vaccine used in New Zealand. While affirming the importance of putting in place carefully-considered safety studies of these new

vaccines, the Committee was reassured by the absence of evidence of an excess of serious adverse events following vaccination with existing meningococcal B vaccines.

#### Guillain-Barré Syndrome (GBS) and vaccination

GBS has occasionally been observed in temporal association with vaccination. This association has been considered as causal in GBS cases following administration of the vaccine against Swine influenza and vaccines against rabies which have been derived from rabbit brains and other nervous tissues. Cases of GBS have also been reported in temporal association with other vaccines, including seasonal influenza, tetanus, meningococcal conjugate and diphtheria-tetanus-pertussis vaccines. Thus far a causal relationship has not been established, other than for Swine influenza vaccine and the aforementioned rabies vaccines.

GACVS recommended large-scale studies of the incidence of GBS before and after immunization. All cases would need to be carefully ascertained and documented. Improved understanding of the pathogenesis of all forms of GBS will help in the determination of possible associations between GBS and immunization. Such studies would be particularly helpful for the investigation of such neurological adverse events following immunization with pandemic or pre-pandemic influenza vaccines.

*The report of the meeting was published in the WHO Weekly Epidemiological Record on 25 January and has been posted on the GACVS web site at [http://www.who.int/vaccine\\_safety/en/](http://www.who.int/vaccine_safety/en/)*

## Eudravigilance training

Helena Sjöström and Lovisa Sällstedt from the Safety Reporting team at the UMC recently attended one of the regular DIA London training courses for reporting via the EMEA (European Medicines Agency) reporting interface, EVWEB. Agencies in the member countries of the European Union (EU) are required to submit ADR reports (in E2B-format) to the central EMEA database, Eudravigilance.

Questions of compatibility of systems are currently of concern in terms of availability of some EU ADR reports to the WHO database. The course allowed Helena and Lovisa to understand better the functionality of the EMEA reporting procedures, and hopefully to provide better support to these countries.

*the UMC is also endeavouring to obtain permission to receive ADR cases reports directly from the Eudravigilance system and this is currently under negotiation.*



## The Italian system of Pharmacovigilance

### Characteristics and perspectives



Mauro Venegoni

In 2001 the Italian national pharmacovigilance system was restructured following the cerivastatine crisis which had shown some difficulties in the management of a pharmacovigilance problem. As a result, a National Pharmacovigilance Network (Rete Nazionale di Farmacovigilanza – RNF) was set up to collect, analyse, elaborate and share data on adverse drug and vaccine reports. Dr Mauro Venegoni, formerly a hospital physician in Milan, with experience of working with his local pharmacovigilance centre in that region, took charge of the RNF two years ago, and has recently given us a report on the latest situation with pharmacovigilance in Italy.

between local and regional centres and the national unit has helped to strongly reinforce the Italian system of pharmacovigilance.

The large number of local pharmacovigilance settings, while a valuable means of disseminating information and contacting physicians and pharmacists, may at the same time cause difficulties in reproducing standard coding and in the training and updating of so many users. According to Italian law reporting is mandatory for physicians.

#### Reaching out to health professionals

The pharmacovigilance bulletin *Reazioni* was first published in 2007 with six editions in the paper version and 22 on-line versions. *Reazioni* was successful: the paper version went up from 15,000 to 25,000 copies, and each on-line version was consulted by more than 10,000 readers including physicians, pharmacists and nurses. (The agency's website is [www.agenziafarmaco.it/](http://www.agenziafarmaco.it/) then go to Registrazione e Farmacovigilanza.)

Activities over the last two years have obtained good results: during 2007 spontaneous reports increased by 50% (from 6,600 to 9,400), and the overall reporting rate increased from 108 to 165 reports per million inhabitants (although in two regions with 14.5 million inhabitants the reporting rate is more than 350/million).

#### National office in Rome

The RNF offices in Rome are beautifully located on the outskirts of the Italian capital. RNF links the national unit with more than 350 peripheral structures (in teaching hospitals and local health service units), regions and pharmaceutical companies.

Health care professionals have to report observed suspected adverse reactions to the local person responsible for pharmacovigilance (LRP) of the health peripheral structure to which they belong. ADR reports are coded (according to the MedDRA dictionary) and then entered in the national database by the LRP. Each night, reports included daily in the RNF database are electronically transferred into the Eudravigilance database according to the standard ICH E2B.

The RNF includes a dedicated, closed e-mail system, only accessible by authorised users, by which every input or update of reports generates an automatic message to inform the marketing authorization holders and regions about new information. This mail system is also used to send urgent information to all local health units or to hospitals and to share important information concerning drugs and vaccines safety.

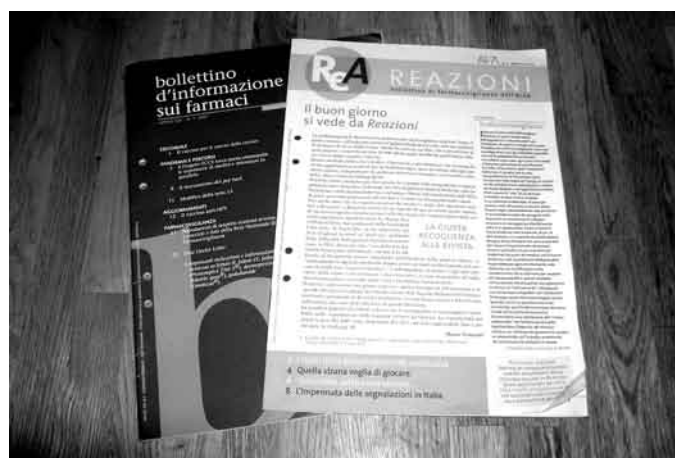
#### Reporting trends

In 2006 the Centre received around 6,000 case reports of suspect adverse drug reactions, mainly from health care practitioners, and a large number of them through one of the regional pharmacovigilance centres or health agencies.

Over the last two years, the Regional Centres have begun to work closely with the National Unit, with the aim of managing the MedDRA coding and performing causality assessment. This co-operation

#### Local and regional activity

The aims of the local centres are to collect the spontaneous reports and to put them into the RNF, to give answers and information to reporters, and to disseminate pharmacovigilance information ('Dear Doctor' letters and other safety information). For this reason, the regional centres aim to control coding quality, perform the causality assessment for serious reactions, plan continuous medical education in pharmacovigilance, and, together with the national centre, to perform data-mining and contribute to the newsletter *Reazioni*.



Italian drug safety journals

The activities of the National Centre consist of the regulatory activity of safety monitoring of the nationally- authorized drugs, and to co-operate with the other national agencies and the European Agency (EMA) for centralized authorized drugs with PSUR analysis, data-mining, etc.

## Intensive monitoring

In Italy some new drugs, such as new antitubercular or innovative drugs, are submitted to intensive monitoring, to collect early the adverse reactions and to evaluate the appropriateness of prescribing them. These drugs are prescribed within a national register, which is monitored by the Agency. At present there are active registers for new antitubercular drugs, dotrecogin, natalizumab, psoriasis drugs (with a programme called 'Psocare'), ivabradine and new antidiabetic drugs (incretines).

For data-mining, data from National network are examined twice a year at a meeting with regional centres: for vaccines also, meetings are planned twice a year, with those responsible for immunisation.

Collaboration with WHO is very important, in particular with the UMC; since 2006 the submission of Italian spontaneous reports, which was interrupted for some time has been restarted from the RNF.

## UMC visitor in Rome

Ronald Meyboom from the UMC visited the Italian national centre on 29 September last year and met the eleven staff members, mainly young, dedicated and well-trained doctors and pharmacists. With a very positive impression of activities in Rome, he is keen for Dr Venegoni to make a visit to Uppsala in the near future to exchange ideas and discuss future plans.



## A bright future

For the future the RNF is implementing patient reporting, which until now has not been developed, and reports from nurses. Furthermore, a 2007 financial regulation which gives 25 million per year to the regions, will help to fund the regions for pharmacovigilance activities, based on achieving active pharmacovigilance projects approved by Agenzia Italiana del Farmaco (AIFA), and other relevant areas in pharmacovigilance. These projects will start during 2008.

*Our thanks to Dr Maura Venegoni for providing much information for this article.*

## ISoP news

Mexico has recently been accepted as a National Chapter within ISoP. Dr Alejandra Rosete of the Pharmacovigilance Institutional Centre at Medica Sur Hospital was the promoter in the country, and is hoping that membership will help to reinforce continuous education to healthcare professionals and also to motivate the health authorities to support and increase their interest in the field.

Dr Rosete is preparing a national pharmacovigilance meeting in November at Acapulco Beach, details of which will be announced soon.

## MedDRA implementation in Vigibase

### Launch of MedDRA implementation in Vigibase and VigiSearch

The Uppsala Monitoring Centre and the ICH MedDRA Management Board have announced the implementation of MedDRA in the WHO global ICSR (Individual Case Safety Report) database (Vigibase). This completes a one-year project between the UMC and the MedDRA Management Board to make Vigibase processes as compatible with MedDRA as they are currently with WHO-ART.

Vigibase is a unique pool of international drug safety data collected from countries participating in the WHO Programme for International Drug Monitoring going back as far as 1968, and currently comprises almost 4 million ICSRs. Member countries have access to the collected data and analyse it in order to investigate potential Adverse Drug Reaction (ADR) signals. Single reports, statistical reports and line listings can also be requested by pharmaceutical companies and academia.

### MedDRA use expands

Prior to this project, all reported ADRs were coded and entered into Vigibase using WHO-ART. MedDRA terms received by the UMC were converted to WHO-ART before entry into Vigibase.

With MedDRA fast becoming the standard coding terminology in the ICH regions and beyond for coding ADRs, indications and disease information, MedDRA-coded data is now being received from an increasing number of countries. Implementation of MedDRA in Vigibase is seen as an important step in increasing Vigibase's use for signal detection, whilst ensuring the integrity of MedDRA-coded safety data.

With the implementation of MedDRA, data can now be entered directly into Vigibase in either MedDRA or WHO-ART, while all Vigibase outputs can be made to display data in either MedDRA or WHO-ART, or in both terminologies. In addition, Standardized MedDRA Queries (SMQs), used to aid in the identification and retrieval of potentially relevant reports from MedDRA-coded databases are also in the process of being implemented.

The launch of the MedDRA implementation in Vigibase includes also general improvements to the search tool as an enhanced query tool, supporting tree browsing and multiple selections of terminologies and drugs, and the possibility to shift terminology in the output; along with statistical presentations, line listings and improved print-outs of the case reports in pdf format.

### The enhanced query tool in VigiSearch

It is possible for a user to choose which terminology to use in a query and in statistical presentations. The query tool supports tree-browsing, and multiple selections of terms in the MedDRA terminology as well as in WHO-ART. The query tool also has a drug/substance browser, allowing the user to browse information on drugs/substances. It is also possible to browse for drugs using the ATC classification.

### Advanced view

The query tool also allows for multiple selections of report details such as causality, outcome, dechallenge and rechallenge. It will also be possible to include co-reported reaction terms.

### Statistical presentations and line listings

The result is presented in MedDRA or WHO-ART but also in parallel when appropriate, depending on the terminology used in the query. The individual case reports will always have information of both the terminologies and the original reported term, when available.

### Assignment of codes

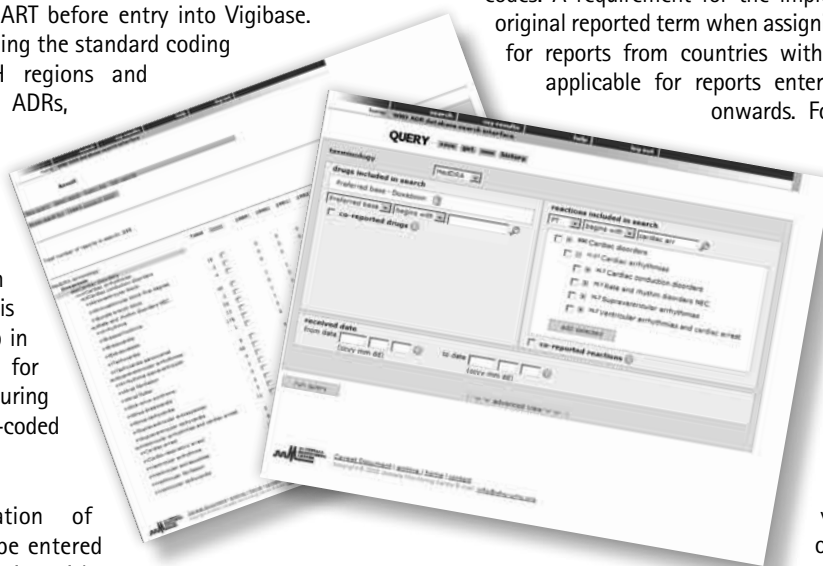
All ICSRs in the database have been assigned MedDRA and WHO-ART codes. A requirement for the implementation has been to use the original reported term when assigning MedDRA and WHO-ART codes for reports from countries within the ICH regions. This rule is applicable for reports entered in the database from 2003 onwards. For reports entered before 2003, current WHO-ART codes have been used for the assignment for reports from both ICH countries and non-ICH countries.

### Mapping the data from WHO-ART to MedDRA and vice versa

The mapping of terms from WHO-ART to MedDRA and vice versa is based on text matching of terms; terms with the same text have been matched to each other. Terms which are not identical have also been matched to each other by the same lexical meaning. The official WHO-ART to MedDRA bridge table, has been used in this mapping process combined with auto-coding rules from the database built up from previously mapped MedDRA to WHO-ART terms.

When searching the database by terms that are equal in MedDRA and WHO-ART the result set may still differ as the terminologies are different, both in structure as well as in number of terms.

*The full press release from the UMC and the ICH MedDRA Management Board may be downloaded from the UMC website (under 'What's New').*





# Latest developments in the Drug Dictionary

## DD Browser

The WHO Drug Dictionary Browser was introduced in 2006. This tool made it possible to access the latest version of the WHO Drug Dictionaries over the internet – with a number of useful search features. The search features in the browser were designed to facilitate both simple searches and more advanced analysis. The advanced features are sometimes necessary when a trade name appears more than once in the dictionary, with different active ingredients.

No local software installation is needed and all system updates are made automatically. With the WHO Drug Dictionary Browser users always get access to the latest version of the Dictionary.

In the latest version of the Browser some new features have been added to the search module, and it is now possible to access both the latest version of the Dictionary as well as old versions – which is sometimes necessary in clinical trials.

## Investigation of non-unique names

An important issue in the development of the WHO Drug Dictionaries is to find tools to simplify the coding of non-unique names, drug names that for different reasons appear with different active ingredients in the Dictionaries.

A revision of all non-unique names in the WHO Drug Dictionary has recently been made. Sometimes drug names appear several times in the dictionaries – because they exist with different active ingredients in different countries and pharmaceutical forms. Many of these have been reviewed in order to identify unnecessary non-unique names, eg non-uniqueness caused by inconsistent coding of salt variations or excipients. This review will continue during 2008. In the 2008 versions of the Dictionaries a number of previously non-unique names have been simplified for coding.

## Keeping in contact

The WHO Drug Dictionaries continue to grow as new features and services are developed. The user group community is suggesting new developments and participates in prioritization of new projects. To participate in the discussions and influence the future features and services please sign up at the WHO Drug Dictionary User Group Portal: <http://usergroup.umc-products.com/>

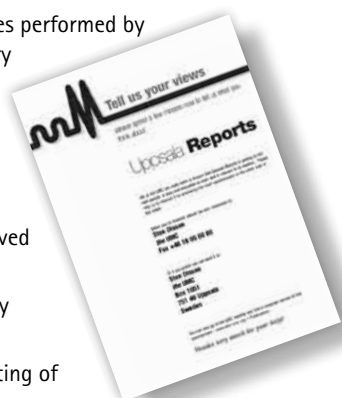
## User Group Meeting

The WHO Drug Dictionary User Group has face-to-face meetings twice a year. This year's European meeting is to be held at Zürich Airport, Switzerland, on 30 May. For more information about this meeting, please log in at the User group page at <http://usergroup.umc-products.com/>. WHO Drug Dictionary subscribers can also easily register as a User group member there.

# UR survey – thanks for the responses

Thank you to all those who sent in a response to our short feedback questionnaire. The results show a pleasing level of satisfaction with Uppsala Reports, although there were requests for different areas of coverage, including :

- pharmacovigilance activities performed by the pharmaceutical industry
- patient Safety
- medical Error statistics
- herbal drugs and phytopharmaceuticals
- statistics about ADRs received by UMC
- pharmacoenvironmentology
- activities for promotion of awareness regarding reporting of adverse drug reactions.



We would remind our readers that the [WHO Pharmaceuticals Newsletter](#), prepared in collaboration with *the* UMC, is an essential guide to latest drug issues arising within the WHO Programme, and that Uppsala Reports does not cover the same ground as this Newsletter. Go to

<http://www.who.int/medicines/publications/newsletter/en/index.html> to download copies.

We will be keeping the survey live on the web ([www.who-umc.org](http://www.who-umc.org) > Publications > Uppsala Reports), and be accepting paper responses until the end of May 2008, and would very much welcome any further comments.

## A month of learning in Buenos Aires

### Encountering pharmacovigilance at the sharp end

*Anna Celén*

Through my desire to learn more about the daily work at a National Centre, as well as improve my knowledge of the Spanish language, I set off for Argentina on the 1<sup>st</sup> of February. The plan was to attend a language course at the University of Buenos Aires in the mornings and spend the afternoons at ANMAT, the National Centre in Argentina. I must admit it was an added bonus to leave the cold and dark Swedish winter behind and step off the plane into summer.



*Maximiliano Bergman, Anna Celén, Beatriz Cardoso and Viviana Bologna at the ANMAT office*

The Spanish course was tough, especially since I was not used to the Argentinean way of speaking, but I learnt a lot during the course. It was also a privilege to be able to practise the language everyday at ANMAT and also get the chance to learn the vocabulary used in pharmacovigilance, something which will definitely be useful in future working relations.

### Pharmacovigilance in Argentina

At ANMAT I undertook a rotation around different departments to learn about their work, achievements and challenges, but I spent the majority of the time in the 'Departamento de Farmacovigilancia' (Pharmacovigilance department) which consists of two services. Viviana Bologna, Head of 'Servicio de Información de Medicamentos' (Medical Information Service), made an interesting presentation about the organisation and the National System of Pharmacovigilance, created in 1993. It currently involves 65 regional centres as well as drug companies which contribute to a great extent. I also read a number of bulletins, published for professionals and consumers, to learn more about this subject.

### Reporting trends

Within this service the staff handle the incoming ADR reports, and Maximiliano Bergman showed me the routines of data input and

causality assessment. There is a common ADR reporting form available but some reporters use their own forms. ANMAT received 3,804 reports during 2007 and the annual report number has been increasing ever since the start of the programme. The reports received include lack of effect, quality defects, medical errors, vaccine reactions and complaints about the information in package inserts. ANMAT has separate databases for the different kinds of reports. Unfortunately only reports with serious and unexpected reactions are currently sent to *the* UMC due to lack of resources. ADR reporting in general is not mandatory for health professionals in Argentina, but there is a programme of intensive pharmacovigilance of drugs for which reporting is mandatory. At the moment, thalidomide and clozapine are included in this programme, and the drug isotretinoin will probably be included in the near future.

### Safety and efficacy

My next task was to learn more about the work in the other service: 'Servicio de Seguridad y Eficacia' (Safety and Efficacy) where Beatriz Cardoso is the Head. She and another member of the team, Claudia Santucci, ably demonstrated their work illustrated with different cases. 15-20% of the reports received by ANMAT are related to quality problems, and the majority relate to lack of effect. The process of investigation to find the reason behind a certain defect is very exciting since it's similar to being a detective. Sometimes it's difficult to conclude if the defect occurred during manufacture or as a result of improper storage or use. If a patient suffered from an unwanted reaction, it's also important to read the SPC of the drug to find out whether the reaction was due to the drug itself or to a quality defect. Drug samples received by ANMAT are sent to 'Instituto Nacional de Medicamentos' (INAME; National Institute of Medicines) which is the laboratory of quality control where tests are performed to see if a drug complies with the specifications. If it does not comply, regulatory actions are taken. I had the opportunity to visit INAME as well as to 'Instituto Nacional de Alimentos' (INAL; National Institute of Food Products) where food products are analyzed. Regarding drug quality, ANMAT is also running a programme concerning illegal and counterfeit drugs. The amount of illegal drugs has decreased remarkably since the launch of the programme in 1997.



*Anna by the stunning Perito Moreno glacier in southern Patagonia*

## Daily work with staff

During my stay at ANMAT I also learned about the process of registration and approval of new drugs. I attended the weekly staff meetings where issues of current interest were discussed as well as a meeting with drug companies to discuss the nimesulide issue. I made a presentation about 'Communications in Pharmacovigilance' and I worked with Maximiliano Bergman on the translation of VigiFlow into Spanish. I also had an interesting conversation with Inés Bignone, Head of the Pharmacovigilance Department, about controversial drugs, challenges and future aims. One important goal is to increase the awareness of the national pharmacovigilance system and thereby increase the reporting rate. Another goal is to enhance its function as an independent source of drug information which serves health professionals as well as the public.

In any free time I had I experienced life in Argentina, among other things visiting a gaucho ranch, spent a weekend in the Misiones province to meet my SOS sponsored child, and seeing the amazing glaciers in southern Patagonia, as well as the end of the world, Tierra del Fuego.

I want to express my gratitude towards all staff at ANMAT, particularly the staff at the Pharmacovigilance Department, and especially Inés Bignone for inviting me, Maximiliano Bergman for being my number one guide and generous friend and Claudia Santucci for also spending time with me on the weekends. The experiences I have gained at ANMAT will be very valuable for me in the future. I won't forget the wonderful time spent in Buenos Aires, the warm atmosphere in the office, the delicious empanadas for lunch and the improvised tango in the streets. I will most certainly go back, sooner or later.

## Double ISoP in Thailand

The International Society of Pharmacovigilance organised two parallel courses on 17-18 March in Bangkok. Both were hugely successful with a large and keen attendance.



*Some of those responsible for organising the very successful ISoP meetings in Bangkok, including Wimon Suwankesawong (centre), Kenneth Hartigan-Go, Sophie Spence, Nicholas Moore and Pravich Tanyasittuntorn*

The 25 participants on the 'Pharmacogenetics and Drug Safety' course came from Australia, China, France, India, Indonesia, Philippines and United Arab Emirates as well as Thailand. The 'Basic Concepts' course was attended by 63 participants (half of them from outside Thailand) from 13 countries. Local experts were complemented on the teaching faculty by members of the ISoP Executive Committee.

ISoP is now looking forward to its annual meeting on 5-8 October 2008 in Buenos Aires, Argentina (<http://www.isop2008.org/>)

## WHO Advisory Committee

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) held its fifth annual meeting at WHO headquarters, Geneva, 25-27 February 2008.



*All the members of the WHO Advisory Committee at their February meeting in Geneva*

The extensive agenda had many topics of a principal nature but some problems specific to individual medicines were also discussed. Since medicine safety is relevant to many of the disease-oriented WHO programmes there were presentations from and discussions with representatives of several of WHO's public health programmes. Discussions were also held regarding the principles for reporting to Vigibase and the conditions for a widening access to, and an optimized use of the database.



## *the UMC back under one roof*

*Anette Sahlin reports*

After over 10 years at Stora Torget – the main square – in central Uppsala, increased staff meant that *the UMC* had to find a new home. With colleagues split over two sites time, energy, and internal cohesion were being lost. So after much viewing of possible new premises around Uppsala, planning started during the autumn on merging the two offices at one location on Bredgränd in the pedestrian area of central Uppsala.

A couple of weeks before Christmas we had 500 boxes delivered to Stora Torget and another 200 boxes to the other office and so the great packing adventure began. During this time staff found lots of interesting stuff that had been stored (or just forgotten) over the years. Among other things, our signal reviewer Ruth Savage's shoes turned up – again. The same shoes she had forgotten when she visited some years before, and which she was able to use when she visited again in November 2007.

After lots of discussions on how to place the departments and individual staff in the new premises we closed the computer network on Friday 25<sup>th</sup> January and over the weekend moved everything out of the old offices to Bredgränd.



*The weekend unpacking operation*

The efficiency of the removals firm NFB was amazing; it took them less than 12 hours to empty Stora Torget on the Saturday, and all the equipment at the other office was moved even faster during the Sunday. While the NFB people did all the carrying some members of UMC staff unpacked as soon as the boxes started to arrive, so that when Monday came most of us could just start work as normal.

In mid February we found one last missing box (one person was on vacation so she didn't realize that she got one extra box that in fact belonged to someone else), and NFB picked up 688 empty flattened boxes, so now we are officially 'Moved In' at our new home!

### **Other staff news**

Congratulations are due to Malin Jakobsson who recently presented her Master's thesis '[Vaccine pharmacovigilance in the WHO database](#)', at the Faculty of Pharmacy, University of Uppsala, her supervisor being Niklas Norén of *the Uppsala Monitoring Centre*.

The purpose of this thesis was examine different aspects and challenges of vaccine safety surveillance in the WHO database, in particular, general differences in characteristics between individual case safety reports related to synthetic drugs and vaccines, respectively; the usefulness in vaccine surveillance of automated knowledge discovery methods developed for ADR surveillance; and the coverage of terminologies for medical products and adverse reactions with respect to recent publications on emerging vaccine safety issues.

Helena Sjöström, who has been a key member of the Safety Reporting Team since 2000 has recently got married and as a consequence changed her surname to Wilmar – so **Mrs Helena Wilmar** is the same person, although many people will also know her as Tova!



*The building which includes the new UMC office, with neighbours Swedish Radio.*

# Introducing new staff

*We are please to introduce several new staff members working across the UMC.*

## Jessica Avasol

Jessica is from a small west-coast island just north of Gothenburg, with a population of 300 inhabitants swelling to 3,000 in summer, when visitors come to their holiday homes.

Jessica joined *the UMC* as a Sales Assistant, helping customers of the WHO Drug Dictionary, WHO-DD Browser and training courses, with special focus on the validation reports and limited study licenses applications. "As Katarina Hansson is on maternity leave, I am now responsible for the day-to-day work in the sales group."

Jessica has two children Karl, six and Ludvig three and a half. "I am in love with my house and garden and am currently doing my best to get a feeling for gardening. Although not too successful, I am a pro at mowing the lawn!"



*Carl, Lovisa, Malin, Anette and Jessica*

## Carl Huddénus

Carl Huddénus began working for the Centre in 2007 with production of the WHO Drug Dictionary and other database products. He recently changed to Assistant Product Manager where his work is co-ordination and development of projects relating to new products and services.

Graduating with a Master's in Pharmacy from Uppsala University he worked for two years as a hospital pharmacist on the island of Gotland, where he was also on the local pharmaceutical committee, before joining *the UMC*.

"I grew up in Strängnäs, a small town by Lake Mälaren in Sweden. I live in Stockholm but my girlfriend and I will soon move to Uppsala, so outside work I mostly pack moving boxes these days. As a result of a bet made on New Years Eve I will swim two outdoor distance swimming competitions this summer. To be able to pull through the competitions, I play floor ball (almost weekly) for *the UMC* team."

## Malin Jakobsson

Malin, who has recently joined the WHO Drug Dictionary team at *the UMC* is originally from the Baltic island of Åland, Finland.

"In January 2008 I finished my pharmacy studies and started working full-time at *the UMC*, having undertaken my Master's thesis here. I have been working occasional hours for three years at *the UMC* while studying to become a pharmacist."

Her main hobby outside of work is horse-riding which she does several times a week.

## Anette Sahlin

"I was born and raised in the countryside outside Uppsala, and even though I have done some travelling this is where my heart is."

Anette's background includes a variety of employers from her first job as a gymnastics teacher for small children via part-time work at a petrol station to an assignment at GE Healthcare in 2006.

She came to *the UMC* initially to help out with the office move. "My administration skills are various, but I enjoy computerized information storage (databases) and the library at *the UMC* will probably take some time to update now that we have moved everything."

"In my spare time I am building my own house together with my son (aged 12), and when I get tired of hitting my own thumbs instead of the nails, I read, or work in the garden. This winter I also developed a minor addiction to the online game 'Runescape', where I am farming my way towards a skill cape."

## Lovisa Sällstedt

Lovisa grew up outside Katrineholm, a town southwest of Stockholm. She came to Uppsala for university studies, and now calls it 'home'. "On completing my MSc I worked in pharmacies, after which I returned to university for studies in clinical trials. Since I had a special interest in pharmacovigilance (from working at the Swedish Medical Products Agency during my studies) I did not hesitate applying to *the UMC* when I got the chance!" Lovisa works in the Reporting Team in the Safety Support and Services department – supporting national centres in their ICSR reporting to the WHO database. She is also currently involved in the development and validation of next version of VigiFlow.

"In winter I like cross-country skiing while in summer I try to make time to play golf. I love spending time in my family's cottage in the northern part of Sweden, fishing and looking for old books in flea markets. What impressed me when starting at *the UMC* was the warm atmosphere among colleagues. I enjoy the mix of different people working here which contributes to the good working spirit."

## Visitors flock to *the* UMC

A delegation from the **Japanese Ministry of Health, Labour and Welfare (MHLW)** spent a few hours at *the* UMC on 25 February 2008. UMC staff gave short presentations on the WHO Programme, UMC activities, Data Mining in Vigibase and VigiFlow. Dr Tetsuya Kusakabe, deputy director of the Safety Division (Pharma-ceutical and Food Safety Bureau) gave a brief introduction to the Japanese post-marketing safety scheme and also informed us about on-going projects and future plans. Discussions



*Magnus Wallberg (UMC), Takuya Noro (Safety Division), Dr Hideto Yokoi (PMDA), Dr Tetsuya Kusakabe (Deputy Director, Safety Division), Helena Wilmar (UMC)*

on how to handle and insert data with Japanese characters into the WHO global ICSR database, E2B-related issues, as well as Medical and Drug Dictionaries were other topics discussed throughout the morning.



*Sten Olsson and Patrick Zuber*

Dr **Patrick Zuber**, representing the Quality Safety and Standards (QSS) team of the WHO Department of Immunization, Vaccines and Biologicals visited *the* UMC on 25 January 2008. Dr Zuber was recently appointed QSS team leader and wanted to become more familiar with the operations of the WHO pharmacovigilance programme. We reported in UR40 (p17) that WHO has decided to support a position at *the* UMC to focus on vaccine vigilance. The details of an agreement between WHO and UMC were discussed during this visit.



*Paul Lalvani with Lovisa Sällstedt*

Executive director of the RaPID pharmacovigilance initiative (see UR39, p6) Mr **Paul Lalvani** visited *the* UMC from 4–6 February 2008. He interacted with various relevant UMC resource persons and got hands-on training on the essentials of the VigiFlow case management tool (see picture).



*Helena Sköld and Professor Stergachis*

Dr **Andy Stergachis**, Professor of Epidemiology and Global Health, University of Washington, Seattle, USA visited Uppsala and *the* UMC on 18 February. Professor Stergachis was provided with a general overview of activities within the WHO Programme for International Drug Monitoring. This formed a background to discussions regarding the joint WHO/University of Washington project for development of a global strategy for pharmacovigilance, supported by a grant from the Bill and Melinda Gates Foundation (see UR40 p17).



*Dr Knight*

Dr **John Knight**, senior medical advisor of Benefit Risk Management of Johnson & Johnson Company visited the UMC on 14 March 2008. Dr Knight is assigned by his company to support pharmacovigilance capacity-building in countries, especially in Asia. Discussions were held regarding possible collaboration in pharmacovigilance training, particularly in India and China.

UMC signal reviewer and former senior medical officer at the Swedish Medical Products Agency Dr **Ingrid Trolin**, visited us on 4 March. She provided relevant UMC staff with an update regarding modern vaccines and safety issues that might emerge as a result of their properties and the manufacturing processes.



*Daniela and Anna Celén*

Dr **Daniela Stanciu**, chief pharmacovigilance officer at the Romanian National Medicines Agency in Bucharest, visited *the* UMC on 4 April 2008. Romania has not submitted ICSR reports to Vigibase for many years and the main part of her visit was devoted to discussions on how that might change.



*Martin Kulldorff with Andrew Bate*

On the bonus day of 2008, 29th February, *the* UMC was honoured by a visit by Dr **Martin Kulldorff** from Harvard Medical School in the USA. He gave a well-received presentation on statistical methods for surveillance of vaccines, which was followed by an interesting discussion.



Dr **Rick Fraunfelder**, Director and Associate Professor, Oregon Health and Science University, Portland, USA and UMC signal reviewer visited *the UMC* on 3 March 2008. As part of a European trip he came briefly to Uppsala where he had meetings with several UMC staff as well as giving an excellent presentation to staff on 'Ophthalmic drug toxicities



*Ralph Edwards with Rick Fraunfelder*

and Pharmacovigilance in ophthalmology', including the reporting system for ophthalmological adverse drug reactions managed by the Casey Eye Institute, and some interesting recent signals. He also gave *the UMC* a copy of the new book *Current Ocular Therapy* by FH Roy, FW Fraunfelder and FT Fraunfelder.

A group of staff from the **WHO Collaborating Centre for Drug Statistics Methodology in Oslo**, Norway visited *the UMC* on 12-13 February to discuss their ATC classification and how it may be best used in the Vigibase database and in the WHO Drug Dictionaries.



*WHO Collaborating Centre for Drug Statistics Methodology in Oslo, Norway visitors with UMC staff in Uppsala*

## New Papers from *the UMC*

Lindquist M.

### **The Need for Definitions in Pharmacovigilance.**

*Drug Safety*, 2007, 30 (10): 825-830.

This article is a review of current definitions and terms commonly used in pharmacovigilance. It argues that such terms should be considered critically with a view to reaching agreement on a preferred term that everyone will use. The author concludes that if international agreement is achieved, the resulting greater clarity of communication should benefit all who are engaged in pharmacovigilance.

Strandell J, Bate A, Lindquist M, Edwards IR.

### **The Swedish, Finnish, Interaction X-referencing drug-drug interaction database (the SFINX group).**

Drug-drug interactions – a preventable patient safety issue?  
*Br J Clin Pharmacol*, 2007, 65:1, 144-146.

Bate A, Lindquist M, Edwards IR.

### **The application of knowledge discovery in databases to post-marketing drug safety: example of the WHO database.**

*Fundamental & Clinical Pharmacology*, 2008, 22: 127-140.

This article looks at the increasing size of spontaneous reports data sets, on which computational capability has increased, and quantitative methods have been increasingly applied. The process of knowledge discovery in databases (KDD) as it applies to the analysis of spontaneous reports can be exemplified by routine use on the WHO ADR database. New adverse effects first highlighted by the KDD process on WHO data include topiramate glaucoma, infliximab vasculitis and the association of selective serotonin reuptake inhibitors (SSRIs) and neonatal convulsions. The KDD process has improved the ability to highlight previously unsuspected ADRs for clinical review, and such techniques will be increasingly used in the successful screening of other healthcare data sets in the future.

Alj L, Touzani MDW, Benkirane R, Edwards IR, Soulaymani R.

### **Detecting medication errors in pharmacovigilance database: Capacities and limits.**

*The International Journal of Risk and Safety in Medicine*, 2007, (19):187-194.

Norén G Niklas, Sundberg R, Bate A and Edwards IR.

### **A statistical methodology for drug-drug interaction surveillance.**

*Statistics in Medicine*, 2008, Wiley InterScience  
(www.interscience.wiley.com) DOI: 10.1002/sim.3247.

This paper examines a shrinkage observed-to-expected ratio for exploratory analysis of suspected drug-drug interaction in ICSR data, based on comparison with an additive risk model. It argues that the limited success of previously proposed methods for drug-drug interaction detection based on ICSR data may be due to an underlying assumption that the absence of interaction is equivalent to having

multiplicative risk factors, and provides empirical examples of established drug–drug interactions highlighted with a proposed approach that go undetected with logistic regression. A database wide screen for suspected drug–drug interaction in the entire WHO database is carried out to demonstrate the feasibility of the proposed approach.

Edwards IR.

## **The future of pharmacovigilance: a personal view.**

*Eur J Clin Pharmacol*, 2008, 64(2): p173–81.

A wide-ranging review of the history, current challenges and proposals to changes to ways of working in pharmacovigilance.

Edwards IR.

## **The Author's Reply.**

*Drug Safety*, 2008. 31(2): p. 182–3.

This letter comments on the response (or lack of) to the problem of whether there is any causative relationship between statins and central or peripheral neurodegenerative diseases and the incidence of any such association. Ralph Edwards argues that this is an unresolved matter which would benefit from a formal study – potentially with a pilot protocol published in *Drug Safety* for comment so that this challenge can be dealt with expeditiously with the best global pharmacoepidemiological expertise.

Bate A.

## **Bayesian confidence propagation neural network.**

*Drug Safety*, 2007. 30(7): p. 623–5.

Describes the current state of data mining of the WHO ADR database at the UMC.

Bate A, Edwards IR.

## **Data Mining Techniques in Pharmacovigilance.**

In: Hartzema AG, Tilson HH, Chan KA, eds. *Pharmacoepidemiology and Therapeutic Risk Management*. Cincinnati, Harvey Whitney Books Company, 2008: 239–272.

(Chapter in a major new textbook)

Derijks HJ, Meyboom RHB, Heerdink ER, De Koning FHP, Janknegt R, Lindquist M, Egberts ACG.

## **The association between antidepressant use and disturbances of glucose homeostasis: evidence from spontaneous reports.**

*Eur J Clin Pharmacol*, 2008;64:531–8.

Do antidepressants cause hypo- or hyperglycaemia?

In the literature a handful of case histories have described the development of either hypo- or paradoxically hyperglycaemia in patients using an antidepressant. A recent review by Jeroen Derijks and colleagues in Utrecht and Uppsala of about 2,500 case reports in Vigibase of derangements in glucose homeostasis reported in suspected connection with one or another antidepressant drug, confirms that hypoglycaemia and also hyperglycaemia in suspected connection with antidepressants are reported to pharmacovigilance centres around the world. Compared to benzodiazepines, both hypoglycaemia (ROR 1.5; 95%CI: 1.20–1.93) and hyperglycaemia (ROR 1.8; 95%CI: 1.40–2.42) were more frequently reported.

Classifying antidepressants in four clusters, based on different patterns of receptors affinities, the association with hyperglycaemia was most pronounced for antidepressants with corresponding affinity for the 5-HT<sub>2c</sub> receptor, histamine-1 receptor and norepinephrine reuptake transporter (clusters 2 and 3). The association with hypoglycaemia was stronger for antidepressants with corresponding affinity for the serotonin reuptake transporter (clusters 1 and 2), while cluster 4 was not associated with disturbances in glucose homeostasis.

To coincide with the publication of:

Lundgren J and D:AD.

## **Transcriptase inhibitors and patients enrolled in the [www.thelancet.com](http://www.thelancet.com)**

Published S0140-6736(08)60423-7. The UMC has made accessible on its website the original text from *Signal* May 2005 which is referenced in the Lundgren paper.

## **AIDE MEMOIRE –**

**Por una estrategia nacional que garantice medicamentos seguros y su uso apropiado.**

The WHO has produced a short 'Aide Memoire' for Pharmacovigilance. Previously available in English, French, and Russian versions, a Spanish language translation has now also been made and can be downloaded in Adobe pdf format from UMC website (under Publications). Mariano Madurga, Head of Co-ordination Service of Spanish Pharmacovigilance System supervised the translation of this document.

# COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
26-29 April 2008	The International Society for Pharmacoepidemiology (ISPE) 2008 Mid-Year Meeting	Boston, USA	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com <a href="http://www.pharmacoepi.org/">http://www.pharmacoepi.org/</a>
21-22 May 2008	Compliance in Pharmacovigilance and the role of the EU QPPV	London, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
29-30 May 2008	VIII Jornadas de Farmacovigilancia	Murcia, Spain	Consejería de Sanidad de Murcia, and Spanish Medicines Agency <a href="http://www.farmacovigilancia2008.es">www.farmacovigilancia2008.es</a>
4-5 June 2008	Periodic Safety Update Reports (PSURs)	Fareham, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
9-11 June 2008	Basic Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 730071 Fax: +44 (0)1483 730008 <a href="http://www.management-forum.co.uk">www.management-forum.co.uk</a>
18-19 June 2008	How to operate Volume 9A	London, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
22-26 June 2008	DIA's 44th Annual Meeting	Boston, USA	DIA Tel: +1 (215) 442 6100 Fax: +1 (215) 442 6199 E-mail: dia@diahome.org
24-27 June 2008	IV National Workshop of Drug Surveillance	Havana, Cuba	National Co-ordinating Unit: Tel: +53 537 206 5603 Fax: +53 537 202 3513 E-mail: giset@mcdf.sld.cu
2-3 July 2008	Introduction to Pharmacoepidemiology	Fareham, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
9-11 July 2008	Medical Aspects of Adverse Drug Reactions	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
4-8 August 2008	Curso de Farmacovigilancia: análisis y gestión de riesgos (Pharmacovigilance training course: Analysis and Risk Management)	La Antigua, Guatemala	Spanish Medicines Agency in collaboration with the Spanish Agency for International Cooperation for Development E-mail: fvigilancia@agedmed.es Web: <a href="http://www.aecid-cf.org.gt/">www.aecid-cf.org.gt/</a>
17-20 August 2008	24th International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Copenhagen, Denmark	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com Web: <a href="http://www.pharmacoepi.org/">www.pharmacoepi.org/</a>
10-11 September 2008	Back to Basics in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
24-25 September 2008	Critical Appraisal of Medical and Scientific Papers: How to read between the lines	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
6-8 October 2008	8th Annual Meeting of ISoP	Buenos Aires, Argentina	International Society of Pharmacovigilance Tel/fax: +44 (0)20 3256 0027 E-mail: <a href="mailto:administration@isoponline.org">administration@isoponline.org</a> Web: <a href="http://www.isop2008.org">www.isop2008.org</a>
15-16 October 2008	Risk Benefit Assessment in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
24 October 2008	Impacting patient safety: Adverse drug reaction signal detection - Quantitative and qualitative approaches in screening healthcare data	Uppsala, Sweden	The Uppsala Monitoring Centre E-mail: <a href="mailto:info@who-umc.org">info@who-umc.org</a> Fax: +46 65 60 60 80 Web: <a href="http://www.who-umc.org">www.who-umc.org</a>



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