

# UR44

UPPSALA REPORTS January 2009

For everyone concerned with the issues of pharmacovigilance

**WHO Programme meeting report**

**Mining the WHO database**

**New members and associates**

**Signal reviewers gather**

**Books**



# DIRECTOR'S MESSAGE



Ralph Edwards  
Director  
the Uppsala Monitoring  
Centre

There are paradoxes and challenges in the pharmacovigilance in public health programmes. I have been involved in reviewing some malaria projects recently which emphasised that the following situation still exists, despite several efforts within WHO to change it.

Combinations of artemisinin and (usually) old antimalarials (ACT) are very actively promoted. They are the most effective treatment of life-threatening malaria but already there are signs of resistance developing to the all important artemesia derivatives, especially important in the case of the more dangerous falciparum malaria, hence the need for combinations. There is an urgent need to both use ACT widely and also protect them from resistance developing.

ACT are new in the sense of being untested in combination and being combined with relatively toxic, old antimalarials, which in turn have little safety information to modern standards. The combinations have had relatively limited field experience (eg in subjects with malnutrition or having common co-morbidity such as HIV/AIDS): most studies are relatively small efficacy studies.

So far there has been little evidence of risk management planning by even the major pharmaceutical industry suppliers, and, amongst major donors of funding for the provision of ACT, there has been either no provision for pharmacovigilance in their plans or confusion about what should be done. This has resulted from the paramount view that the priority is to, 'get the products out there'.

Some of the experts in malaria are now concerned about safety issues with ACT, though the realisation has been relatively, but reasonably, late. The reason for this is that for years they have been working with very limited funding and seeing the ravages of malaria. Now they have money for research on malaria, its treatment and the monitoring of effectiveness of treatment. After having these other matters under some control, safety becomes a significant consideration for them, and they have money to tackle it. This has led to certain groups considering safety in the same way as malaria efficacy control: from a laboratory and epidemiology perspective. This is leading to suggestions that large controlled clinical trials should be done to determine the possible risk of, say amodiaquine hepatitis (risk order 1: 10 000) and that patients who have ADRs should have blood level monitoring, and that all subjects should have haematological and clinical chemistry measurements. These proposals are laudable in one sense, but are they necessary or cost effective?

One challenge with the monitoring of effectiveness or safety in malaria therapy in real life is that many of the most threatened patients are children and that they will be repeatedly treated, probably several times a year. Current studies for (sustained) effectiveness are relatively small and short, answering the question of whether patient sample effectiveness is maintained. Pooling the safety data from small, short studies, not designed for safety, will not answer the safety issues which may exist about idiosyncratic adverse events such as hepatitis when there is repeated exposure, and may not even disclose whether the drugs remain effective in those individuals repeatedly using them.

We have proposed cohort event monitoring (CEM) as a signal detection method in areas where there is no established pharmacovigilance system, the aim being to have a reasonably sized cohort (around 10 000) of patients followed up for a reasonable period (1-2 years) which would be an acceptable substitute for the reporting of ICSRs in developing countries. This would not be a signal *analysis* system, but would give a supportable level of confidence that harm with ACT would be detected, and with quantitation, which is better than conventional pharmacovigilance reporting systems, though only the targeted drugs are covered. Any concerns about new or known signals that need evaluating should be done in specifically targeted and powered studies, but CEM has the capability of demonstrating whether the older drugs have the safety profile that has been supposed on limited, previous experience.

The paradox is that some seem to want signal detection and validation to proceed *pari passu*, increasing the ethical issues, complexity and cost of studies by inclusion of adequately monitored controls. It is interesting that the same people have argued that long term follow-up of patients is too costly and too difficult. This further perplexes and deters the industry and other funders of antimalarial treatment who are already grappling with costs and supply chain issues, amongst others.

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photo: Maasmechelen/Thorsten Buchen



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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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Uppsala Reports © *the* Uppsala Monitoring Centre 2009

Editors: Sten Olsson and Geoffrey Bowring

ISSN 1651-9779



## Meeting of minds in Uppsala

The global drug safety family gathered for its annual reunion in Uppsala last October. There are three main strands to the formal proceedings of these meetings: lectures on current issues or updates in safety, working groups on a variety of subjects and problems of current interest where proffered papers on safety topics are presented and discussed by participants. The scientific side is important but complemented by the social, with contacts made and working relationships forged. The organisers strive to make the meeting as interactive and participative as possible; evaluations of this year's events praised the welcoming and business-like atmosphere.



Marie Lindquist

Director of the Medical Products Agency in Sweden. Ralph Edwards, Director of the Uppsala Monitoring Centre welcomed everyone to a meeting celebrating the 40th anniversary of the WHO Programme for International Drug Monitoring and 30th anniversary of the UMC, and especially guests David Finney and Ed Napke who had been involved in the Programme at its start. Hans Hogerzeil, Director of the Department of Essential Medicines and Pharmaceutical Policies, WHO, spoke about the enormous growth of the Programme in the last few years and expressed gratitude to the UMC for their achievements and support. Björn Håkansson, President of the Swedish Thalidomide Society gave a powerful account of the thalidomide disaster in which 12,000 children (of whom 5,000 survived) were born with congenital abnormalities.

### 40 years of safety monitoring

Kees van Grootheest recounted the early years of pharmacovigilance, from the thalidomide disaster to several countries setting up of ADR reporting systems. In the 1980s René Royer from France introduced the term 'pharmacovigilance' on the international scene. WHO Programme achievements were highlighted: the creation of definitions and standards, the use of IT and statistical approaches in improving signal detection, increased emphasis on communication and transparency, attention for herbal drugs (main treatment for much of the world's population) and pharmacovigilance in developing countries.

### Evolution of WHO Programme and UMC

Marie Lindquist and Ralph Edwards presented WHO Programme landmarks over the last 30 years. Looking forward, the priorities were

supporting WHO in safety activities, increasing quality and quantity of Individual Case Safety Reports (ICSRs), patient safety instead of drug safety (including medication error), signal detection and analysis using new data sets, and improvement of communication between all stakeholders.

### Strategy for the next 10 years

A plenary contrasted perspectives from USA and Togo viewpoints. Gerald dal Pan underlined that an ideal pharmacovigilance system should detect and assess signals rapidly and accurately, promote the safe use of medicines, manage the risks of medicines judiciously, communicate timely and useful information to patients and practitioners and actively engage all stakeholders. The ideal signal detection system should make use of multiple data sources and automated signal generation. The need for high-quality spontaneous reports will not reduce: automated systems will complement, not replace them. Signal assessment will put more focus on careful safety data collection in clinical trials – both pre- and post-approval, improving the quality of spontaneous reports, assessing safety throughout a drug product's life-cycle, contribution of population-based data to signal assessment and standardization of healthcare data to allow more efficient signal assessment.

Another task is to promote the safe use of medicines via better information and risk management, as well as development of new methods of signal detection and assessment from population databases, better methods of identifying who should or should not receive a medication, evidence-based risk management strategies and communication. Social challenges (convincing society that this is an important endeavour) and financial challenges (funds sufficient to conduct all these activities) were also described.

The perspective of Edinam Agbenu from Togo was that while the majority of countries believe that pharmacovigilance is an important activity, lack of interest and resources make it difficult to conduct drug monitoring. Her suggestions to improve pharmacovigilance included integrating systematic pharmacovigilance in drug registration; running national pharmacovigilance centres as a prior public health programme, develop spontaneous reporting, influence curricula in health science teaching institutions, innovation in strategies for communication in pharma-covigilance and the creation of small networks. There is a need for tools for system evaluation, funding to operate and opportunity to start.



Mohammed Hassar

Though details differ, there were many similarities between the two countries, the importance of pharmacovigilance and the need for effective strategies.



Sten Olsson

### Global overview

Sten Olsson presented preliminary results from a global survey of pharmacovigilance activities in low- and middle income countries. Results were based on responses from 55 countries, and will be formally published later. Helena Wilmar gave an overview of reporting-related issues at the UMC. Vigibase has more than 4.3 million ICSR reports. Countries may submit reports either in the 'old WHO format' or the newer E2B format; 48 countries currently submit reports in E2B (24 of which use VigiFlow). The UMC have

developed a new Vigibase import process (see UR42), and a backlog of E2B cases was now uploaded (see p9). In recent years a decline has occurred in the number of ADR reports from European Union countries; most cannot send to Eudragilance and the WHO simultaneously, and choose to send their reports to Eudragilance only.

### WHO updates

Shanthi Pal, Essential Medicines and Pharmaceutical Policies, WHO reported on progress from recommendations made by working groups in Buenos Aires (2007), some of which had been taken forward by the Advisory Committee on Safety of Medicinal Products (ACSoMP) in 2008. Micheline Diepart, Jackson Sillah, Lembit Rägo and Adwoa Bentsi-Enchill also gave progress reports on important work at WHO.

Working group discussions covered a diverse range of topics (see box).

### Working Groups

- The need for new and updated definitions in pharmacovigilance
- Indicators for measuring development and impact of pharmacovigilance
- Towards a global approach for vaccine crisis management strategy
- Trends in the safety of herbal medicines
- Acting on pharmacovigilance data for better decisions on benefit and harm
- Special training needs to promote patient reporting
- Better use of national databases for intensive analysis of case reports
- Implementing strategies for medication errors

### Plenary sessions

Andrew Bate (UMC) gave two key talks: data-mining of longitudinal patient records and maximization of signal detection capability, and an update on CIOMS VIII 'The application of signal detection and signal management in pharmacovigilance', whose objective is to provide points for consideration to manufacturers, regulatory authorities, and international monitoring centres wishing to establish a systematic and holistic strategy to better manage the entire 'life-cycle' of a drug safety signal.

Anders Rane of the Karolinska Institutet, Stockholm examined the particular problems of promoting safety of medicines in children,

### Problems of current interest

- Quadrivalent HPV Vaccine
- Pediacel
- BCG SSI® vaccination
- Serious hypersensitivity reactions following DTP vaccine
- ALS and statins: a Rapid Response analysis
- Rimonabant and psychiatric adverse reactions
- Osteonecrosis of the jaw and bisphosphonates
- Antipsychotic drugs and hypothermia
- Olanzapine and cardiomyopathy
- Low Energy Impact Fractures under Long Term Biphosphonate Therapy
- HMG-CoA-reductase inhibitors and interstitial lung disease
- Emerging safety signals for leflunomide combination therapy
- Serious ADR caused by illegal products adulterated with glibenclamide
- Copalchi (*Coutarea latiflora*): a new hepatotoxic herbal remedy?
- Pharmacovigilance pilot study in HIV/AIDS, TB and malaria programmes
- Stevens-Johnson Syndrome (SJS) with Sulphadoxine-Pyrimethamine (SP)
- Foetal Resorption Induced by Artesunate
- Active pharmacovigilance project, direct reporting by health professionals
- Unfractionated heparins and impurities

which are often prescribed off-label and unlicensed. A Europe-wide study in five hospitals found that 46% of all drug prescriptions for children concerned unlicensed drugs or off-label indications. He looked at the obstacles to the development of medicines for children and issues related to post-marketing monitoring of safety of children's medicines.

### Drug safety in Sweden

On the last morning Gunilla Sjölin-Forsberg and colleagues from the Swedish Medical Products Agency gave a wide-ranging talk. The Swedish ADR database, created in 1965, contains more than 100,000 reports. An MPA campaign on illegal drug sales was presented by Kerstin Hjalmarsson (96% of on-line medicines traders operate illegally and sell counterfeit drugs, and 62% of the prescription-only medicines purchased over the internet are counterfeit or substandard). Qun-Ying Yue then spoke about the Eudragene project, a multi-centre European case-control DNA collection for ADR study.

At the close, two delegates gave their impressions. Bushra Elnagar from Sudan, attending his first National Centres Meeting, extended his thanks to the organization for making it possible for so many people from so many countries to come together and learn more about pharmacovigilance. Pia Caduff Janosa from Switzerland, who first attended a National Centres Meeting in 2003 and has been present at all meetings since, also expressed her gratitude for the warm atmosphere and thanked all the UMC staff especially those not in the spotlight. She encouraged participants to take the chance to share experiences with this group.

### To the next meeting

Mohammed Hassar from Morocco invited everyone to Chellah in 2009 and showed pictures of the city and the staff at the Moroccan pharmacovigilance centre. Ralph Edwards and Sten Olsson, who chaired the organizing committee (and had only missed one meeting in 30 years), thanked staff at the UMC for their work during the week. This was the biggest meeting ever held with more than 120 delegates from more than 55 countries.

## Namibia's safer medicines challenge

Namibia's national drug policy of 1998 recommended establishing a drug information centre and an adverse reaction monitoring unit, to co-ordinate adverse drug reaction reporting, and manage data collection, analysis and dissemination. In 2003, a project report (led by the Ministry of Health and Social Services (MOHSS) in Namibia) highlighted the lack of a formal medicines information centre and national system for monitoring and reporting adverse medicine reactions; both of which are a serious impediment to promoting the rational use of medicines.

To address this, in 2006, a working group under the leadership of the MOHSS developed an implementation plan detailing the office set-up, functions, staffing, and resourcing for Namibia's Therapeutics Information and Pharmacovigilance Centre (TIPC). The Centre was established in 2006 integrating therapeutics information and pharmacovigilance activities into a unified service.



*Participants and facilitators of the 2nd National Therapeutics Information & Pharmacovigilance Centre (TIPC) training, Windhoek*

The TIPC's mandate is to improve the rational and safer use of medicines in Namibia. It is the MOHSS's official centre for the provision of unbiased therapeutics information and pharmacovigilance services to health care professionals and the general public. The Centre comes under the secretariat of the National Medicines Regulatory Council (NMRC), and is located at Windhoek Central Hospital. The TIPC organization includes a co-ordinator, a medicines information pharmacist, a technical advisor and a library assistant; there is also a part-time medical officer trained in pharmacovigilance and medicines information.

### Functions of the TIPC

The Centre receives and responds to therapeutics enquiries by phone, fax and e-mail. A quarterly therapeutics information bulletin (Namibian Medicines Watch) and the Centre's web-page on the NMRC website are used to disseminate topical therapeutics information. Information to the general public is mainly geared to medicines used in public health programmes, particularly anti-retroviral, anti-tubercular and anti-malarial medicines. Basic information is communicated via newspapers, brochures, posters, videos and other media.

TIPC has drafted comprehensive guidelines for monitoring the safety of medicines, which include spontaneous reporting of adverse events, cohort event monitoring in public health programmes, periodic safety updates and monitoring of herbal medicines. Reports have already started trickling in from different sources including health care professionals using ADR reporting forms to detail information on suspected adverse reactions to medicines and product defects. There is an effort to establish a patient reporting system.

### Spontaneous ADR reporting by health professionals

Three rounds of national training on pharmacovigilance have been conducted for health professionals; more than 60 participants from all the 13 administrative regions of the country attended. A presentation on the importance and benefits of monitoring and reporting adverse reactions to medicines has been incorporated in all training and orientation materials for therapeutics committees.

### Integrating information and medicine safety

The TIPC's web-page on the NMRC website ([www.nmrc.com.na](http://www.nmrc.com.na)) as well as Namibia Medicines Watch are used as two-way communication media on medicines efficacy and safety between TIPC, the NMRC, therapeutics committees, the health care provider and the general public. Reporting forms and forms to request therapeutics information can be downloaded from the site.

The TIPC also uses promotional materials such as branded clinical coats for health care professionals and other items to create awareness and remind health professionals and the public about TIPC services.

TIPC staff sit on the Essential Medicines List Committee, to provide safety and efficacy information for the evaluation of medicines for inclusion to or deletion from the Namibia essential medicines list. Similarly, TIPC is involved in systematic reviews to guide treatment guidelines development.

### TIPC Launch

TIPC was launched on the 12<sup>th</sup> of May 2008 with the theme "know your medicines".



The launch was attended by over 100 guests, comprising top Ministry officials of the Republic of Namibia, representatives from health-related organizations, public and private health care professionals from all regions of Namibia. Special guests came

from the Uppsala Monitoring Centre in Sweden: Ralph Edwards and Sten Olsson shared their global outlook on medicines safety. The event was fully covered in the national media.

### TIPC at the Annual Meeting of National Centres

TIPC participated in the 31<sup>st</sup> National Centres Annual Meeting for the first time, as well as the UMC's pre-meeting orientation tutorial and the one-day signal detection conference after the meeting in Uppsala.

### A strong start

Gradually, TIPC is putting together a strong national medicine safety monitoring and therapeutics information system. So far, it has laid the foundation for a robust pharmacovigilance system, collecting,

compiling, analyzing and using the information collected. The number of ADR reports received is increasing but is still very low and the quality of the reports also needs improvement. In November TIPC celebrated an important milestone, being admitted as the 90th member of the WHO Programme for International Drug Monitoring.

# Pharmacovigilance in Kazakhstan



*Seated front left to right: Dr Zhan Abilayuli, Dr Gulnara Berdimuratova (General Director of the National Center), Svetlana Kil (domestic manufacturers)*

*Behind: Dr Abrec Sariev, (National Academy of Sciences), Kuzdenbaeva Raisa, Akmaral Kabdenova MSc Pharm (Director of test centre, National Center), Valentina Shnauksha MSc Biology (chief of bioequivalence laboratory), Dr Zhannat Satibaldieva (Director of Immunobiology), Dr Ardak Tulegenova (Director of pharmaceutical centre, National Center).*

Kazakhstan is situated in Central Asia, deep in the Eurasian continent. Its territory covers 2,724,900 sq km (1,049,150 sq miles) – it is the second largest country in the Commonwealth of Independent States and the world's 9<sup>th</sup> largest country, but with a population of 15 million. Kazakhstan's 12,187 km border touches China, Kyrgyzstan, Turkmenistan, Uzbekistan and the Russian Federation.

The capital is Astana and there are 14 administrative regions, 84 cities, 159 districts, 241 towns and 2,042 aul (rural villages). Kazakh is the official language but state institutions and local administration also use Russian.

The National Center for Drug Expertise, Medical Practice and Medical Equipment, Republic Governmental Enterprise Ministry of Public Health (or simply the National Center) is the state expert organization for medicinal products. Created by governmental order of October 2002 (website [www.dari.kz](http://www.dari.kz)), the General Director is Dr Gulnara Daumovna Berdimuratova.

The National Center implements public health services for safety control, efficiency and quality of pharmaceuticals, with the following functions:

- carrying out expert activities for state registration of drugs, items of medical practice, medical equipment;
- standardization of pharmaceuticals;
- information and publishing activities;
- expertise in the promotional materials on medicinal preparations;
- leading on projects of laws, state standards, technical rules, certification of pharmaceuticals;
- expertise in the protocols and reports of non-clinical and clinical research into pharmaceuticals;
- ADR monitoring.

The National Center structure includes twelve regional branches around the country, where accredited technical centres carry out technical and other checks.

The head office is in the city of Almaty, and has a full range of laboratories covering all aspects of pharmaceutical regulation, a pharmacopeia centre, a pharmacological centre (in which is situated the department of ADR monitoring), a department for study of items of medical practice and medical equipment, a certification department, legal department, an information department, and archive.

The National Center publishes the scientific – practical reference-book 'The Pharmaceutics of Kazakhstan', news of state registration of drugs, laws concerning the registration of drugs, results of ADRs, and scientific research in the field of medicine. In each edition of this reference-book a doctor, pharmacist or the customer can always find a 'yellow card' to report ADRs.

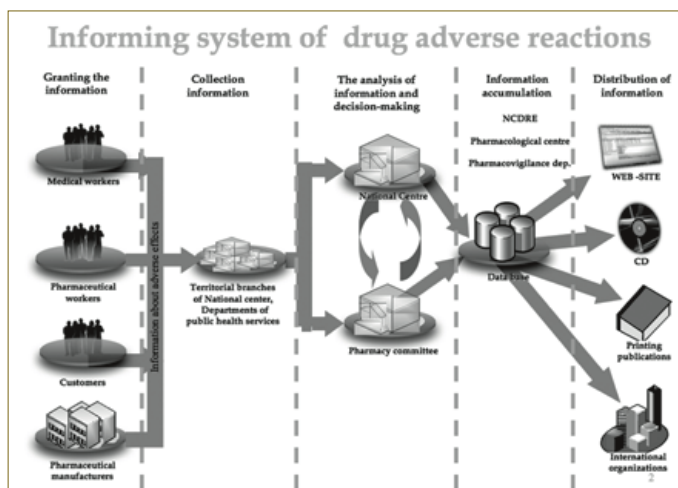
Monitoring of side effects of drugs is carried out according to legislation first dating from January 2004 and expanded since, with an order 'The Instruction on realization of ADR monitoring' from February 2005 and one on 'About organization of ADR monitoring' (designating the National Center as the authorized organization for reports about side effects of the drugs) in May 2005.



To increase the responsibility of domestic and foreign manufacturers in the control of safety of medicinal preparations registered in Republic of Kazakhstan, and to harmonize with the international requirements in pharmacovigilance areas, a guideline and order of the Ministry of Public Health entitled 'The form of the periodic safety updated reports of medicinal preparations for the pharmaceutical manufactures' was passed in April 2007 and updated in August 2008

# NEW MEMBERS

where the applicant for a marketing authorisation is required to provide a detailed description of their system of pharmacovigilance and, where appropriate, of the risk management system.



*The reports on the detected cases of ADR under the scheme indicated.*

Since May 2005 the department of monitoring has mounted 27 seminars about pharmacovigilance and methods of detection of ADR signal with participation of more than 4,000 doctors, pharmacists and nurses. The training was conducted by Dr Raisa Kuzdenbaeva and Dr Zaure Aitbayeva. From 1 May 2005 to 30 November 2008, 994 cards reports have been collected in the database of the department of ADR monitoring. Kazakhstan is a full-member of WHO Programme for International Drug Monitoring since July 2008.

## Pharmacovigilance in Andorra

*Cristina Vilanova Serrano*



*Cristina Vilanova Serrano and a colleague in the Andorra pharmacovigilance centre*

Andorra is a small country in the Pyrenees, between France and Spain, with a population of 83,000. Andorra has no pharmaceuticals industry and pharmacies import medicines mainly from Spain and France, but also from other countries.

In January 2008 we started the pharmacovigilance programme with a presentation of the programme to health care workers and a speech of Professor Joan-Ramon Laporte, director of the Fundació Institut Català de Farmacologia in Spain about adverse drug reactions and their impact on public health (see UR41).

During 2008 we joined the WHO Programme for International Drug Monitoring as an associate member and on 30 September WHO informed us that we had become the 89<sup>th</sup> full member of the WHO programme. Due to our size, we just have a national centre (without regional centres), in the Ministry of Health, Health Care Resources Service, with two pharmacists working part-time.

This first year we have received 72 ADR reports, many more than we expected, most from the pharmacy service of the Andorra hospital, whose pharmacists are very interested in pharmacovigilance and do an important job monitoring the safety of medicines. Apart from their reports, several Spanish drug manufacturers have reported to us adverse reactions of their drugs that affected Andorran people. We have received few reports from physicians, and have to work in order to create a culture of ADR reporting.

In 2008 we have provided up-to-date information on adverse reactions to professionals. In 2009 our ministry will have a new web site ([www.msbfh.ad](http://www.msbfh.ad)), which will be very useful as a tool to communicate messages about the safety of drugs. After one year working in pharmacovigilance, we know that our main weakness is a lack of training in analysing and codifying ADRs. Next year we will organise some training sessions focused on this.

## Other new countries

In addition to Andorra, Kazakhstan and Namibia, we hope to offer a feature on the new national centres in Sierra Leone, Ethiopia and Sudan, which have become full members of the WHO Programme during the last few months.

We also report that Senegal and Cambodia have become Associate members of the WHO Programme during the last quarter.

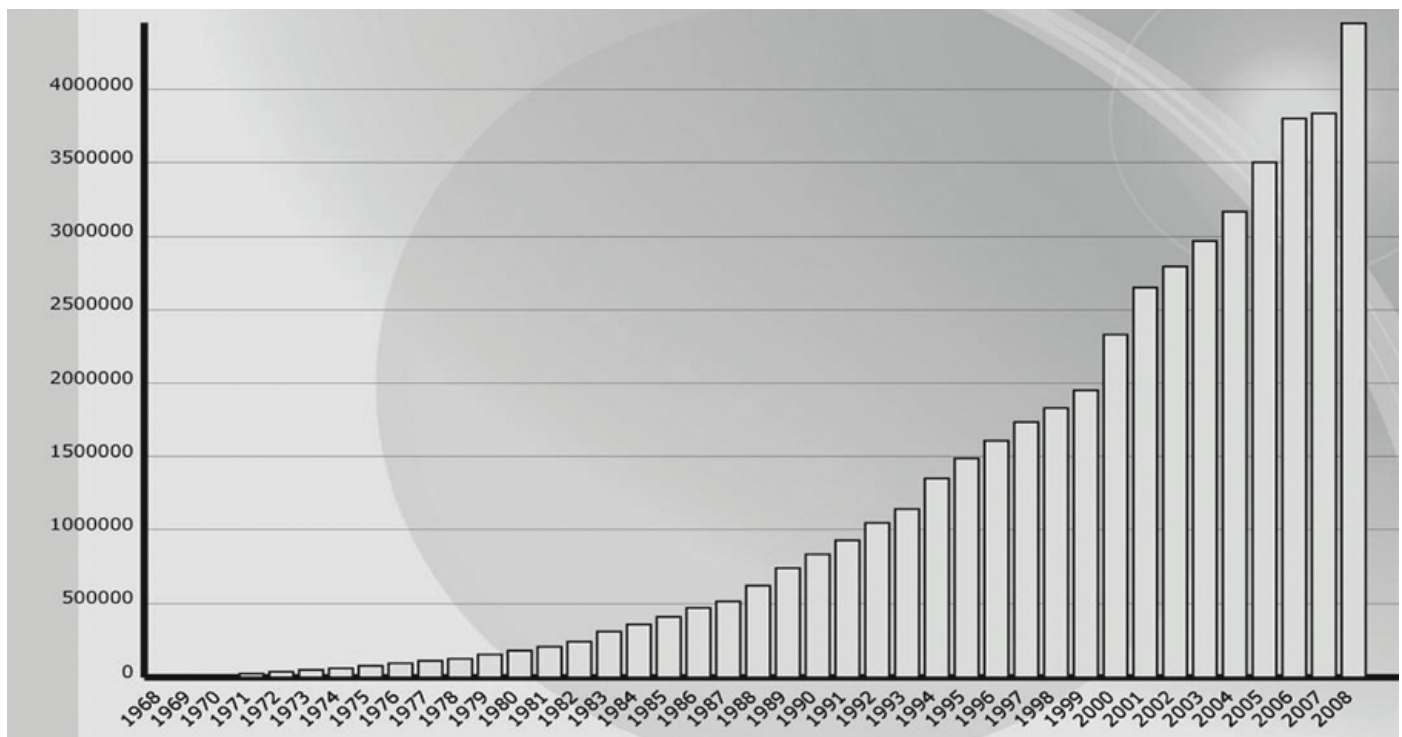


## Backlog of ICSRs now in VigiBase

Helena Wilmar

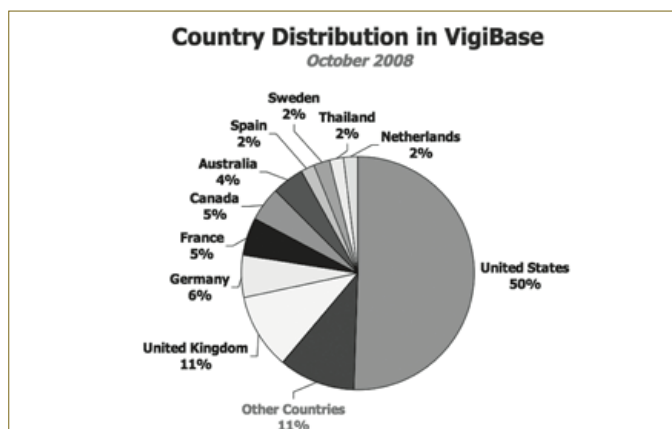
During the 31<sup>st</sup> Annual National Centres Meeting in Uppsala, the issue of a backlog of ISCR cases to be inserted into VigiBase before the end of 2008 was dealt with. This backlog included cases in the old WHO format from 31 member countries. The majority of WHO Programme members report their ADRs in the recommended international E2B-format, but around 40 out of 90 countries are still using this WHO format.

Figure 1



Cumulative number of ICSRs in the WHO global ICSR database 1968-present

Figure 2



Country distribution of ICSRs in VigiBase as of October 2008 (total number of ICSRs = 4.3 million).

A graph showing reports in VigiBase per country, per million inhabitants will be published in UR45.

We are pleased to report that the processing and validation of all the ISCR cases in this backlog was finalized in late November and the cases are therefore now available in VigiBase. Approximately 134,000 backlog cases have been inserted and as a result of the new import process these reports were also converted into E2B.

As the new import process is up and running, the reporting team are now streamlining their routines and will soon start to send out reminders to all member countries not having submitted any ISCR cases in accordance with the WHO Programme requirements.

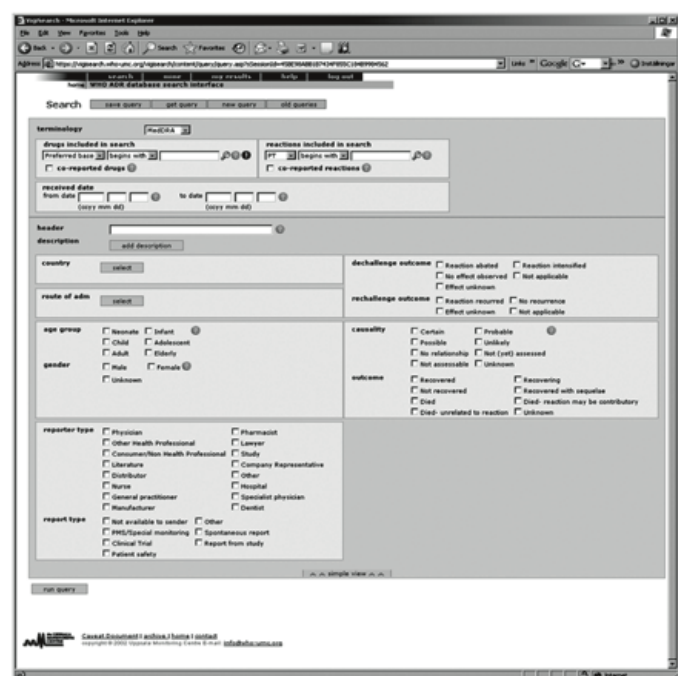
One factor over the last three years has been a noticeable decline in ADR reporting to WHO from European Union countries. Since 2005,

it is mandatory for European Union countries to send ADR cases (and only serious cases) in E2B format to EMEA (European Agency for the Evaluation of Medicines). Therefore many EU countries are still dealing with the development and testing of their new E2B compatible databases in order to create the required reporting format for EMEA and WHO. The situation is compounded by the non-compatibility between EMEA's electronic system 'Eudravigilance' and WHO submission procedures. The Safety Reporting team at the UMC is continuing to work with national centres to ensure that the WHO database is as complete as possible.

## New and improved VigiSearch – VigiMine available at last!

After many years of planning and dreaming of giving the National Centres access to the statistical tools that the UMC uses, we have finally reached a great milestone. The UMC has released VigiMine™ as a new module of VigiSearch™ and hence enabled all users with access to VigiSearch to also view the IC values and other statistics for all drug-ADR pairs in the Global ICSR database, VigiBase.

This step is just the latest in a series of steps taken during the last couple of years to improve the functionality and performance of VigiSearch and more will come.



Screen shot of advanced view in VigiSearch search interface.

### What is VigiSearch?

VigiSearch is a powerful search tool that provides access to all active case reports in VigiBase. All National Centres, both full members of the WHO Programme for International Drug Monitoring and associate members of the Programme, have access to this information. This means that it is possible to find detailed information on (currently) over 4.4 million individual case safety reports. In the simple search mode a user can specify a drug and/or a reaction, and also date criteria. Drugs can be entered at different levels from highest ATC levels to the lowest level (which is the specific trade name of a drug). Adverse reactions can be entered in a similar fashion.

The improvements over the last couple of years include a more extensive search interface in the advanced search mode, more information on an overview level for case reports and detailed pdf printouts, among other upgrades. Enhanced performance has enabled searching for much larger datasets and users' queries will now execute much faster than before.

### What is VigiMine?

VigiMine is a new development within VigiSearch, making the IC values and other statistics available online. It replaces the 'combinations database' which for several years has been distributed by CD to National Centres. The advantages are numerous, including easy access to IC values for ALL drug-ADR pair combinations in the database (not only those of the latest quarter), more frequent updates (currently monthly, but our aim is to have bi-weekly or weekly updates), and the availability of statistics stratified by age, gender, age+gender, country and reporting year. We have also made time-scan data available, ie the development of the IC values over time.

VigiMine may be used for analysing and detecting drug-ADR pairs of interest. Using several filtering and sorting functions it is possible to search for drugs within one or several classes or specific ADR terms or one or several groups of ADR terms. VigiMine makes it possible to get fast answers to questions like: What are the unexpected frequently reported terms (ie IC025 > 0) for all drugs within an ATC group with reports from more than one country, ordered by the number of reports where the reaction is marked with 'rechallenge'? It has never been easier to compare the reporting statistics for all substances within an ATC class with a specific ADR term.

The detailed statistics for a drug-ADR combination allow swift access to general statistics on the reporting of current drug and current ADR. This clearly reveals information about age, gender or country related reporting patterns. The stratum specific IC values may be a help to detect stratum specific issues or assist in exposing confounding, but most important give the user a general view of the reporting pattern for the current drug and current ADR.

VigiMine is a fast and user-friendly tool for getting information on the reporting within a specific area of interest or in general, but can also access more detailed statistics about the reporting on a specific drug-ADR pair using either WHO-ART or MedDRA.

## Advances for online searches in the WHO database

### VigiSearch

- more extensive search interface
- more information on an overview level for case reports
- detailed pdf printouts
- searching for much larger datasets faster than before

### VigiMine

- access to IC values for ALL drug-ADR pair combinations
- more frequent updates (currently monthly)
- statistics stratified by age, gender, age+gender, country and reporting year
- time-scan data available.

The screenshot shows the VigiSearch interface in a Microsoft Internet Explorer browser window. The address bar shows the URL: <https://vigisearch.who-umc.org/vigisearch/content/query/VMQuery.aspx?SessionId=45BE98ABB18743F855C18489984562>. The page title is "VigiSearch - Microsoft Internet Explorer".

The interface includes a navigation menu with "home", "search", "mine", "my results", "help", and "log out". The "mine" section is active, showing a "new query" button and a text box for the Information Component (IC) value: "The Information Component (IC) has been extensively evaluated for its use in signal detection based on the WHO-ART terminology. While in principle IC values should be similarly useful with the MedDRA terminology, this has not been tested in practice by the UMC."

The search filters section includes:

- terminology:** WHO-ART (selected)
- drugs included in search:** ATC - N02BA - Salicylic acid and derivatives
- reactions included in search:** PT (selected), begins with (empty)
- IC >:** (empty), **IC <:** (empty)
- IC<sub>025</sub> >:** 0, **IC<sub>025</sub> <:** (empty)
- N<sub>comb</sub> >:** (empty), **N<sub>comb</sub> <:** (empty)
- N<sub>country</sub> >:** 1, **N<sub>country</sub> <:** (empty)
- number of records displayed:** 50
- only critical terms:**

A "refine" button is located below the filters. The results section shows the following summary:

**Dataset date:** 2008-12-01  
**Number of combinations in result:** 274  
**Total number of reports:** 4 454 666

	preferred base	preferred term	critical	N <sub>comb</sub>	IC	IC <sub>025</sub>	N <sub>drug</sub>	N <sub>adr</sub>	N <sub>country</sub>	N <sub>dechallenge</sub>	N <sub>rechallenge</sub>	N <sub>fatal</sub>
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	FACE OEDEMA	Yes	819	1.09	0.99	29 847	57 279	36	361	60	1
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	ANGIOEDEMA	Yes	934	1.86	1.77	29 847	38 287	42	370	49	6
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	GI HAEMORRHAGE	Yes	4 268	4.28	4.24	29 847	32 716	45	1 539	20	189
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	MELAENA	Yes	3 237	4.68	4.63	29 847	18 714	37	1 113	18	60
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	BRONCHOSPASM	Yes	327	0.77	0.61	29 847	28 560	28	132	17	6
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	OEDEMA MOUTH	Yes	174	1.51	1.29	29 847	9 071	24	35	17	0
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	HAEMORRHAGE RECTUM	Yes	661	3.43	3.32	29 847	9 058	21	128	13	9
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	EPISTAXIS	Yes	640	2.76	2.64	29 847	14 060	28	98	10	13
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	THROMBOCYTOPENIA	Yes	697	0.76	0.66	29 847	61 216	35	148	9	39
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	PURPURA	Yes	495	1.37	1.24	29 847	28 599	40	111	9	13
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	HAEMATEMESIS	Yes	2 053	4.63	4.56	29 847	12 327	35	567	7	85
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	LARYNX OEDEMA	Yes	92	1.28	0.97	29 847	5 600	19	42	5	2
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic acid	ASTHMA	Yes	90	0.36	0.05	29 847	10 430	21	34	5	1
<a href="#">details</a> <a href="#">reports</a>	Acetylsalicylic	ANGIOEDEMA	Yes	54	3.29	2.88	591	38 287	6	20	4	0

Screen shot from VigiMine search interface with filtering options

## Future developments

There are still a lot of functions left to expand within both VigiSearch and VigiMine. Our primary focus in the near future will be on developing new and existing output formats to enable management and printing of the data. Also, functionality such as filtering and sorting are on the agenda. As the UMC continues developing and improving VigiSearch and VigiMine all users are encouraged to communicate their comments and questions on these tools to [info@who-umc.org](mailto:info@who-umc.org) (enter 'VigiSearch' in the Subject). Those that want to apply for access can fill in the application form available at the logon page <https://vigisearch.who-umc.org>.

# THE 40TH ANNIVERSARY MEETING IN PIC



Gunnar Alván (Swedish Medical Products Agency), Ralph Edwards, Hans Hogerzeil (WHO Essential Medicines and Pharmaceutical Policies), Björn Håkansson (The Swedish Thalidomide Society)



Before the start of the conference dinner the assembled were addressed by Carl von Linné



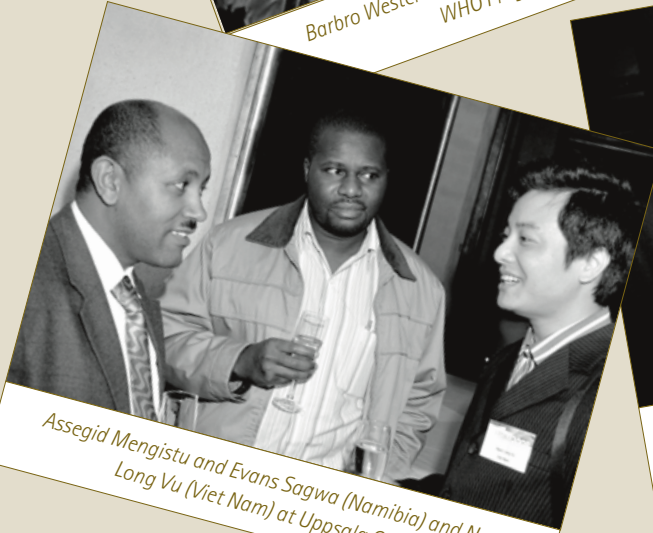
Bruce Hugman (Overall F...  
Björn



Barbro Westerholm speaks about the start of the WHO Programme



All the representatives assem...  
congress centre fr



Assegid Mengistu and Evans Sagwa (Namibia) and Ngoc Long Vu (Viet Nam) at Uppsala Castle



Carl Älfvåg (UMC Board), Gunilla Sjölin-Forsberg (Swedish MPA), and Priya Bahri (EMEA)



The meeting was honoured by...  
Professor Ed Napke with h



... (facilitator) makes a presentation to ... Håkansson



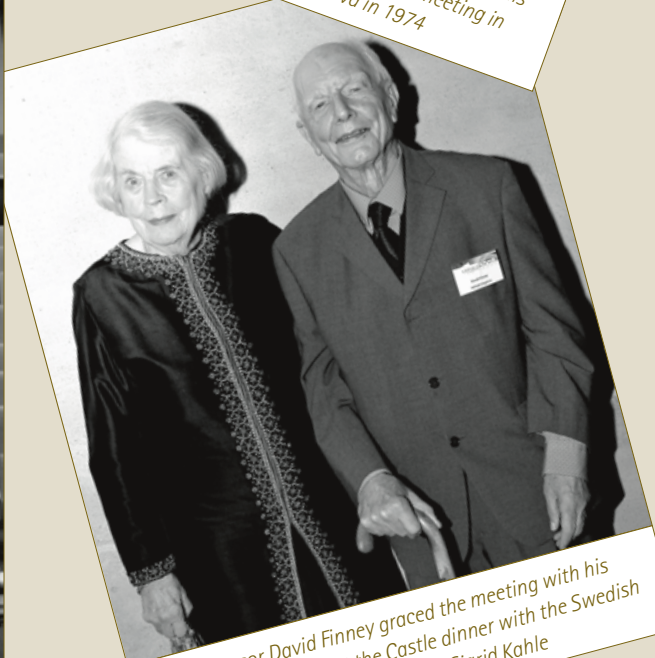
The attentive audience during a plenary session



Ronald Meyboom, who attended his first WHO Programme meeting in Geneva in 1974



... in the concert hall at the ... for the group photo



Professor David Finney graced the meeting with his presence; here he is at the Castle dinner with the Swedish journalist and writer Sigrid Kahle



... by the attendance of ... his wife Gunvor



At the conference dinner, entertainment in song . . .



. . . and dance.

## A full-house for signals

*Ola Caster*

On the 24<sup>th</sup> October, immediately following the 31<sup>st</sup> Annual Meeting of the WHO Programme, a celebratory and indeed unique event was organized by the UMC. The conference was fully booked and demand was so high that we were regrettably unable to accommodate all last-minute applicants. Nonetheless, 150 participants from over 30 countries world-wide gathered in Uppsala's lovely Alfvénsalen to listen, react, and discuss at the open research meeting *Impacting patient safety: Adverse drug reaction signal detection – Quantitative and qualitative approaches in screening healthcare data*.

The programme consisted of seven presentations from distinguished professionals in the field of signal detection, as well as a panel discussion. The presentation sessions were chaired, gently yet firmly, by UMC's Research Manager, Dr Andrew Bate, while the panel was lead by UMC Deputy Director Dr Marie Lindquist.

The first speaker to amaze the audience was Dr Jeffrey Aronson from the University of Oxford. He invited the listeners to a mind-opening journey which started by discussing how definitions can be made in general, and concluded with the announcement of results from recent research activities, proposing a definition of a signal in the context of pharmacovigilance. This was followed by an industry representative, Dr Manfred Hauben from Pfizer in New York. Dr Hauben gave the listeners a fascinating glimpse of the challenges he and his colleagues at Pfizer face in their daily signal detection work, and some of their approaches to dealing with those challenges.



*The packed house at the UMC research conference*

After refreshments, it was time for UMC's most recent PhD, Niklas Norén, to enter the stage giving an excellent overview of the recent ground-breaking research on quantitative methods for signal detection at the UMC, including work on longitudinal patient data. As the senior statistician in the research team Niklas focussed on the quantitative and methodological aspects of signal detection. This contrasted effectively with the perspective taken by the next speaker, Professor Toine Egberts from Utrecht University who, as a clinical pharmacologist, has combined an impressive research career with on-going patient contact. Professor Egberts presented some of his recent leading-edge pharmacovigilance research in the context of the people for which we really work, namely the patients.

After lunch, the audience needed to quickly regain their concentration for the quick-fire diversion by Professor Hugh Tilson. Professor Tilson was a speaker at UMC's anniversary research meeting in 1998, and his talk began with the conclusions from 1998, then looked at the use of large population-based surveillance systems in pharmacovigilance, and continued with an overview of the progress made since then in this exciting field.

The sequence of presentations was temporarily broken for a panel debate on What impact can the UMC have on patient safety? featuring five panellists: Dr Cedric Bousquet (France), Professor Ambrose Isah (Nigeria), Dr Ronald Meyboom (UMC), Dr Ed Napke (Canada), and Dr Ruth Savage (New Zealand). Although the time-frame for the discussion was short, and although lots of people from the audience wished to contribute and ask questions, it seemed clear that the UMC has a secure reputation around the world, and is seen to have a central role to play in the on-going improvement of patient safety.

Towards the end of the day, the participants enjoyed two final probing presentations. First Dr Gunilla Sjölin-Forsberg, head of the Drug Safety Department at the Swedish Medical Products Agency. One aspect of her insightful talk was the breadth of signalling sources that the regulatory agencies need to consider, and the delicate job of balancing the value of each of these, especially when confronted by questions from the public. The day concluded with Professor Stephen Evans from London School of Hygiene and Tropical Medicine. He not only gave an excellent and much-appreciated talk on the current state-of-the-art of quantitative signal detection, in the light of the day's previous presentations, he responded with some insightful suggestions about what might happen in the near future in this field.

All in all, the UMC representatives, the invited speakers, panellists, and the participants seemed to enjoy this event immensely. Given the positive response, and that we were fully booked, we plan to have a similar conference sometime in the future.

*If you were at the meeting, you should have received an e-mail with instructions on how to access the presentations through our website. If you have not received this e-mail, but were at the meeting, please contact us at [info@who-umc.org](mailto:info@who-umc.org).*

# More than a get-together

*Jeanette Johansson*

The UMC's review panel started its work of detecting and analyzing signals in the WHO global ICSR database, VigiBase, in the 1980s. Today the panel consists of more than 40 voluntary expert reviewers from 20 countries, working independently. As the review panel has grown over the years, and new panel members are recruited continuously, the need for meeting together has increased. The previous meeting was held in Uppsala in December 2004.

In October 2008 the fourth review panel meeting was held over a weekend at a conference venue close to the UMC office. It was attended by 27 of the reviewers from 17 countries, some of whom had attended the other UMC meetings earlier in the week. The aim of this meeting was for reviewers and the UMC Signal Detection team to get together, share experiences and gain an understanding of each other's contribution to the signal detection process. Our ultimate goal is to improve our joint work within the area of pharmacovigilance.

## Turning work into action

The UMC Director, Ralph Edwards, welcomed everyone and pointed out that this year's meeting was especially important for turning what we want to do into action. All reviewers were encouraged to feel that they can clearly speak their opinion and to take an active part in the work. Richard Hill, new team leader for the Signal Team, continued with a short presentation of his role and said that he was happy to see so many participants and a good mix of both old and new reviewers. He ended by saying that the Signal Team are open to any kind of suggestions that can improve our daily work.

Next Jeanette Johansson and Maria Tengstrand (Signal Detection Team) gave a short 'walk-through' of the UMC signal detection process. Since all review panel members have great experience within the field of pharmacovigilance but have been on the panel for differing times they have different knowledge of the UMC processes. Therefore this session was held interactively with the reviewers in order to let the signal team and the 'old reviewers' share their experience of review work with the newcomers, so that everybody could be at the same level of knowledge.

Kristina Star (of the UMC Research team) talked about the use of data mining in signal detection. IC (Information Component) is a measure of the disproportionality between the observed and expected values for a drug-ADR combination. She explained how the IC value is calculated and considerations when using the IC; she also touched on the usefulness of viewing the change of the IC over time ('time scans').

After lunch Ruth Savage and Ronald Meyboom gave a double presentation, explaining their view on potential signals and causality assessment: "Pharmacovigilance does not aim at 'knowing everything' but at adding further pieces of information that are important for the safe and rational use of medicines".

The first day ended with Maria Tengstrand demonstrating VigiSearch and VigiMine (see page 10-11 in this issue) and explaining the possibilities of these tools. Each member of the Review Panel has

automatic access VigiSearch/VigiMine. During the following workshop session the reviewers, divided into four groups, selected two or three items from a list of topics and discussed them during the afternoon.



*The members of the UMC signal review panel, with UMC signal team staff above, at the October meeting.*

Later in the evening we had an enjoyable dinner at the UMC office at Bredgränd in central Uppsala. The reviewers got an opportunity to have a closer look at the Centre's premises, get to know each other better, and to meet more of the UMC staff.

## A second day of hard work

The second day started with more discussion from the Saturday afternoon workshops, with the groups reporting back on their chosen topics. After this, Andrew Bate, the UMC's research manager gave an update on recent methodological developments from a research perspective. After coffee Richard Hill briefed the group on the Reviewers website and requested suggestions to improve the site.

The remainder of the meeting was open for topics proposed by the Review Panel themselves which they felt they wanted to discuss more in-depth:

- ◆ Response to Signal from National Centres
- ◆ Drugs of current interest
- ◆ Communication: the UMC – Pharma company and Reviewer – National Centre – the UMC
- ◆ Impact assessments
- ◆ Triage
- ◆ Reviewers website

Overall the meeting achieved a better understanding by the signal team of what information reviewers find useful, and an enhanced awareness by reviewers of the timeframes for the signal detection process and the production of the Signal document. Also, there was progress in the introduction of enhanced and regular communication between reviewers and signal team and documentation of resources that the Signal Team can provide (e.g. additional searches). When the meeting finally closed late in the Sunday afternoon everyone agreed that we want to see each other more often!

## Traditional medicines Mumbai conference

*Mohamed Farah*

A WHO Congress on Traditional Medicine, was held on 7-9 November 2008 in Beijing, China, co-sponsored and hosted by the Ministry of Health and State Administration of Traditional Chinese Medicine.

The objectives of the Congress was to:

- Review the role of traditional medicine and its providers in health care in line with the Alma-Ata Declaration and in the renewal of primary health care
- Review countries' progress in the field of traditional medicines
- Share information and experience in how to integrate traditional medicines into the health system based on primary health care
- Share information related to research, education and practice of traditional medicine
- Promote the proper use of traditional medicines by the population.

This International conference brought together a host of experts from many countries including China, Australia, Belgium, Canada, France, Germany, India, Indonesia, Japan, Kenya, Malaysia, Mexico, Mongolia, New Zealand, Panama, Republic of Korea, Singapore, South Africa, Sweden, Switzerland, Thailand, the USA and UK.

The line-up of speakers was impressive, especially Dr Margaret Chan the Director-General of WHO and Dr Xiaorui Zhang of the Traditional Medicine Team, WHO, Geneva. The Uppsala Monitoring Centre was represented by Mohamed Farah and Henrik Sahl.



*Mohamed Farah, Henrik Sahl, Wu Gui Zhi, Zhang Cheng Xu in discussion at the Chinese National Center for ADR Monitoring.*

After this meeting UMC staff and the National Center for ADR Monitoring in China had a successful follow-up meeting regarding the UMC's collaboration project (see UR43, p10). Attending from the National Centre in Beijing was Deputy Director of Center Zhang Cheng Xu, Director of Division Chen Yi Xin, and Dr Wu Gui Zhi with other staff.

*Kristina Star*

The 1<sup>st</sup> International Conference on Pharmacovigilance & Clinical Data Management took place in Mumbai, from 3-5 November 2008, organised by Symogen and Cognizant. Dr Pipasha Biswas (Director, Symogen Ltd, UK) and Mr Partha Chakraborty (Head, Cognizant) were programme chairpersons with about 160 participants representing students, university faculty, and pharmaceutical industry.

The organisers had brought together well-known speakers in the field: Brian Strom, Nicholas Moore, and Munir Pir Mohammed. I represented the UMC and talked about data mining in pharmacovigilance from an international perspective. Many of the other speakers came from different pharmaceutical companies or universities around the world, including India, of which one was UMC's signal reviewer Professor Nilima Kshirsagar (Maharashtra University of Health Sciences, and G.S. Medical College and K.E.M. Hospital).

Professor Kshirsagar took Dr Susan Bews (President of the Faculty of Pharmaceutical Medicine of the Royal College of Physicians, London) and me to speak at the Health Centre of the Maharashtra University of Health Sciences and Mumbai University Kalina Campus, where Prof Kshirsagar has been involved in starting a MSc course in pharmaceutical medicine. After a working lunch with some faculty members, Susan and I made our presentations for about 70 students. The students that we met at the university and were also attending the conference were very interested and keen to learn about all aspects of pharmacovigilance. Many are trying to find ways to build their competence by seeking employment overseas. Hopefully they will return to India again to build up pharmacovigilance in this country, which is developing rapidly and is an attractive place for pharmaceutical companies to outsource activities.

This conference is a sign that the pharmaceutical industry and other stakeholders within the Indian healthcare system are working hard to develop pharmacovigilance in India, although there is still an uncertainty about the strategy of the leadership of the national system.

## In the Americas

Dr Shanthi Pal, of Quality Assurance and Safety: Medicines at WHO Geneva represented the WHO Programme for International Drug Monitoring at the II Congress of Pharmacovigilance in Acapulco, Mexico and the International Network of Safe Medication Practice Centres (SMPCs) in Oakbrook, Illinois, USA, last November.

The Mexican Congress attracted over 500 students and health-care professionals to improve knowledge in and commitment to pharmacovigilance in Mexico. The meeting identified a need for capacity-building in database techniques at the national centre, which will be addressed by the UMC, and a WHO Consultant will visit and support the Mexican centre.

The third annual meeting of the International SMPC Network in Oakbrook was hosted by the Joint Commission (WHO CC for Patient Safety), and attended by members representing the SMPCs or organizations undertaking related work. Dr Pal presented the WHO Programme, in particular the role of national pharmacovigilance centres in patient safety, and how these centres could work in collecting data on reports of medication errors.



# Synergy in Botswana

Ulrika Rydberg

Botswana is a country that is big in spirit and size, but small in population (only about 3 persons per square kilometre). Much of the country is covered by the Kalahari Desert and the main income is from mining (mostly diamonds), cattle farming and tourism. Botswana became an associate member of the WHO Programme in December 2005 and is now working towards full membership. To complete this process the health workers need to be aware of pharmacovigilance so that they report ADRs. Another need is training of the personnel at the National Centre, the Drug Regulatory Unit (DRU) at the Ministry of Health. In November 2008, a big step was made towards fulfilling these needs.



*The training group in Gaborone*

In most cases, when two groups need training, there would be two separate courses, but in this case this was combined. For two and a half days, both the health professionals and the personnel at the DRU were introduced into the world of pharmacovigilance. The rest of the week was then used for a continuation for DRU personnel and a few others. The course was organised by the DRU in collaboration with the UMC and RaPID. Ralph Edwards, Marie Lindquist and Ulrika Rydberg from the UMC, Dat Tran from RaPID and Sinah Selelo from the DRU were speakers.

The first part of the course was held in Boipuso Hall at a congress centre in the capital Gaborone. The weather was as warm as the reception, and the food served at lunch delicious. Including both the health workers and the people from the DRU for this first half of the week created synergetic effects. The potential reporters could discuss the reporting process and the need for pharmacovigilance in Botswana with the DRU. Many active discussions resulted where constructive input was given directly, both to the DRU and to the health professionals. The topics about counterfeited drugs and how to stimulate reporting were among those that created the liveliest discussions.

Most of the rest of the week was spent at the Ministry of Health, a modern building near the centre of Gaborone. This part of the course gave the DRU personnel time to learn and discuss pharmacovigilance more in-depth. Among the subjects covered were the future of pharmacovigilance in Botswana, the process from signal identification to policy decisions, and training in how to use the ICSR management system VigiFlow.

Later in the week it turned rainy, to the satisfaction of all. Rain is the most valued weather in the dry climate of Botswana, so valued that the currency, Pula, is named after the Setswana word for rain. That this promised to be a good year was seen in the amount of flowers and growing vegetation everywhere. All in all, we had very satisfying week with the teachers also learning a lot from the students!

After spending a nice week of spring in Botswana, those of us from the UMC were met by the first snowflakes of what developed into the very first snowstorm of winter when we returned to Sweden.

## Part of the jigsaw

Cecilia Biriell

In November, Cecilia Biriell and Richard Hill from the UMC attended the WHO/UNICEF Technical Briefing Seminar on Essential Medicines Policies at WHO Headquarters in Geneva. This week-long seminar is held annually, and aims to provide a general understanding across a broad range of medicines issues, particularly those affecting developing countries. Topics examined included National Medicines Policies, the *WHO Model List of Essential Medicines*, medicines pricing, traditional medicines, counterfeit medicines, and of course, pharmacovigilance.

An interesting session on access to medicines in developing countries reviewed the inter-related roles of funding bodies, procurement agents, and the supply chain. Overall, it was clear that pharmacovigilance is just one piece in the large jigsaw puzzle that represents the use (and abuse) of medicines, and it is useful to learn about other aspects of the puzzle in order to put our work into perspective.

Participants included staff from WHO collaborating centres and country offices, other UN agencies, academic institutions, national government agencies, as well as NGOs such as Médecins Sans Frontières. Countries represented included: Afghanistan, Jordan, Sudan, Germany, the Netherlands, Tajikistan, Mozambique, Moldova, and Tuvalu, so there was certainly ample opportunity to learn first-hand about common problems faced by pharmaceutical sectors worldwide.



*Participants at the Technical Briefing Seminar in Geneva*

Further information about future courses can be obtained from the Essential Medicines and Pharmaceutical Policies Department, WHO ([www.who.int/medicines](http://www.who.int/medicines)).

## Users convene at Uppsala conference

The start-up meeting for a User Group for VigiFlow was held on October 20, the first day of the National Centres Uppsala Conference 2008. The meeting was opened and chaired by Magnus Wallberg from the UMC. Almost 30 participants attended the meeting (most of them are already using VigiFlow).

### VigiFlow in use

Pia Caduff-Janosa from Swissmedic introduced VigiFlow and explained how the system is used in Switzerland. During the talk she pointed out that every country using VigiFlow does so differently, and that we were all gathered together to identify solutions.

Swissmedic has a working network of six regional centres using VigiFlow. At the regional centres they enter reports and do a primary evaluation of the case. At the national centre they do a secondary assessment of all reports. At the moment Swissmedic is evaluating the new Administrative tools now available in VigiFlow, and they plan to go live with using it during 2009.

### Version 4.0

Magnus Wallberg made a short description of the new features in VigiFlow 4.0 released on June 12, 2008. Among them was the E2B report management with both import and export (e.g. submissions) of electronic reports in E2B format. VigiFlow now contains many

new fields to be fully E2B compatible. Other new features are the Submission manager, Administrative chapter and the Address book.

### Future release plans

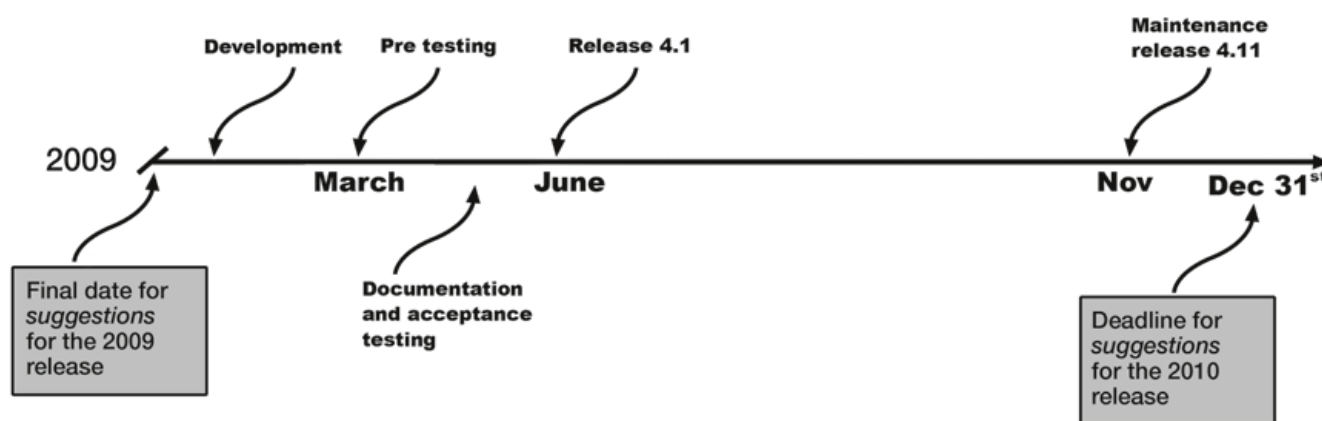
the UMC has decided that there should be no more than one major release of VigiFlow per year - in June, with a possible maintenance release (to fix any errors) in the autumn. The following diagram shows the milestones for the VigiFlow releases during 2009. The same milestones will apply also for subsequent years.

Magnus stressed that all suggestions for improvement are always welcome, and can be sent directly to the UMC, either by using the feedback function in VigiFlow or by sending an e-mail to [vigibase@who-umc.org](mailto:vigibase@who-umc.org).

### Future of the User Group

After the discussion of future development, the structure of the User Group was discussed. There was a positive response to starting a User Group and the meeting participants wanted a yearly meeting to be held in connection with the WHO annual meetings.

For communication in the time between meetings an internet 'community' forum would be set up, co-ordinated by the UMC.



## E2B reporting seal of approval

A UK pharmacovigilance company has successfully tested VigiFlow's E2B capabilities with the UK national centre (MHRA) via the Eudravigilance website.

PV DIRECT has been using VigiFlow over the last seven months and have put it through its paces. Dr Anzal Qurbain of PV DIRECT comments "the database has performed remarkably well and is probably one of the best safety databases I have come across in the industry, VigiFlow is up there with the market leaders".

PV DIRECT has performed due diligence on several internationally recognised safety databases and finally opted to go with VigiFlow because it was easy to use, simple and fulfilled regulatory reporting requirements. Dr Qurbain, who has worked within drug safety in several pharmaceutical companies went on to state that "the combination of a high-quality, low-cost, organization like PV DIRECT using a safety database like VigiFlow demonstrates that pharmacovigilance can be undertaken at an affordable cost".

## Singapore bulletin gives points

The Singapore Pharmacy Council has added the national pharmacovigilance bulletin *ADR News Bulletin* from the Singapore Health Sciences Authority to the list of approved publications which, by reading, pharmacists can obtain continuing professional education points. The bulletin is published three times a year to increase awareness of adverse drug reactions and to promote ADR reporting, as well as to communicate regulatory actions.

Pharmacists in Singapore can apply for a patient care continuing professional education point for having read each issue.

## New publications from the UMC

Edwards IR. Controlled Trials and Risk of Harm. *Drug Safety* 2008, 31(11), 961-963.

In a trenchant editorial, Ralph Edwards tackles the age-old conflict between randomized controlled trials and individual case safety reports.

Hopstadius J, Norén GN, Bate A & Edwards IR. Impact of stratification on adverse drug reaction surveillance. *Drug Safety* 2008, 31(11), 1035-48. With comments following by Stephen Evans and response from the authors.

The original paper investigated the impact of using adjusted observed-to-expected ratios, as implemented for the Empirical Bayes Geometric Mean (EGBM) and the information component (IC) measures of disproportionality, for first-pass analysis of the WHO database.

In *Drug Safety* 2008, 31(10), abstracts 62 and 74 in the section on the 2008 International Society of Pharmacovigilance meeting describe studies from the UMC:

Episodes of Amnesia and other Neuropsychiatric Disturbances during the use of Zolpidem and other non-Benzodiazepine Hypnotics, and

Acute Hypersensitivity Reactions to Andrographis paniculata-containing products, as reported in international pharmacovigilance.

## ISoP news

### Buenos Aires conference

The 8<sup>th</sup> ISoP Annual Meeting in Buenos Aires, Argentina from 5-8 October 2008 organised by Raquel Herrera and Luis Alesso of the Argentinean Society of Pharmacovigilance was attended by over 270 delegates from around the world. The society's General Assembly marked the launch of a Mexican Chapter of ISoP, as well as the nomination of David Coulter and Joan-Ramon Laporte as honorary members. A large number – 178 – of abstracts were proffered as posters and oral presentations, and as ever, prizes were awarded to the three best posters. The committee, chaired by John McEwen, announced the winners as:

1<sup>st</sup> Prize: Cachin N, Kreft-Jais C. 'From an identified risk to regulatory measures: Implementation of HLA-B\*5701 screening before Abacavir treatment'

2<sup>nd</sup> Prize: Pariente A et al. 'Antipsychotic use and myocardial infarction in demented patients treated with cholinesterase inhibitors'

3<sup>rd</sup> Prize: Keller GA et al. 'Pharmacovigilance Unit of the Second Chair of Pharmacology: Review and analysis of 700 notifications received'

### Verona offers three courses

ISoP training courses will take place on 26 & 27 March 2009 at the University of Verona, Italy.



Nicholas Moore, Marie Lindquist, Luis Alesso and Ronald Meyboom at the ISoP conference in Buenos Aires.

- Keeping the lights green – your risk management roadmap
- Ecopharmacovigilance, and
- Basic concepts of pharmacovigilance.

The courses are organized with the ISoP Italian Chapter and full details can be found on the ISoP website [www.isoponline.org/Training](http://www.isoponline.org/Training)

### 2009 Annual Meeting in France

*From Pharmacovigilance to Risk Management*

The 9<sup>th</sup> ISoP Annual Meeting is hosted by the Centre Regional de Pharmacovigilance Reims Champagne-Ardenne from 6 to 9 October 2009 at the Centre des Congrès, in central Reims.

## Visitors

On 26 November 2008 the UMC had the pleasure of receiving three visitors from the School of Pharmacy, University of Addis Ababa, Ethiopia. They were Professor Teferi Gedif, Dean, School of Pharmacy, Professor Kaleab Asres, Department of Pharmacognosy and Professor Ephrem Engidawork, Department of Pharmacology. The three were keen to learn about the details of the collaboration between the UMC and the new national pharmacovigilance centre in Ethiopia and how the School of Pharmacy may support the development of patient safety efforts in the country. Discussions were held about the feasibility of research collaboration between our two institutions.



*The three visiting Ethiopian professors, together with a research student presently studying at Uppsala University*

## The new vaccines post in Uppsala

*Jerry Labadie*, who will take up the post of Vaccine Safety Specialist on the 1st of March, introduces himself:



"I am married with Inger Forsell (a former UMC employee) and live in Amerfoort, Holland. I have four kids, three girls and a boy, aged from 23 to 14. In my spare time I run to keep in shape and sometimes each year participate in amateur races. I like to spend time in our 'paradise' in Sweden, Vappa, a cottage in the countryside, not far from Uppsala.

Vaccines are considered to be one of the most cost-effective healthcare interventions. They are most effective when used in national programmes. Enormous progress has been made in increasing vaccine coverage worldwide, and now the next step should be made: monitor safety and respond to safety issues to maintain confidence. This is a serious challenge at the current stage of development that many immunisation programmes have reached. But this is a challenge that UMC is ready to meet and I am happy and proud to be part of the team that will address Adverse Events Following Immunisations (AEFI). Some of you have met me during the pharmacovigilance courses in Uppsala in recent years during my lectures on AEFI. I am looking forward to continuing interacting with you, answering your queries and supporting your dealings in this specific field of Adverse Drug Reactions."

## Response : « Global support for regional problems? »

This article in Uppsala Reports 43 uses the term 'ASAQ' to refer to all artesunate and amodiaquine combinations. 'ASAQ' is a non-registered name that is widely used to refer to the first fixed-dose formulation of artesunate and amodiaquine, which was developed by sanofi-aventis and the Drugs for Neglected Diseases initiative (DNDi). Many could be confused in reading this article which includes 'ASAQ' to encapsulate a wide variety of artesunate and amodiaquine associations available in Africa, such as co-blister presentations, liquid formulations, and fixed-dose combinations. Some of these combinations are well identified, quality-proven drugs. However, many other brands and presentations are of unproven quality, made by a large variety of poorly identified manufacturers and are licensed in individual countries based on very slim registration dossiers that almost invariably do not include any clinical data.

Evidence of quality is available on only a handful of artesunate and amodiaquine associations sold in Africa. We strongly believe that not all products that claim to be an "artesunate-amodiaquine combination" are well enough characterized to enable pooling of safety data. Each brand must be analyzed separately – only proven-quality brands can, in a scientifically-sound way, be considered as a group as "artesunate-amodiaquine combinations".

Because we know that some adverse events may not be detected in clinical trial settings, and because we know the shortcomings of pharmacovigilance systems in sub-Saharan Africa, sanofi-aventis and DNDi decided in 2007 to set up a proactive monitoring plan of ASAQ safety profile in 'real-life' conditions. With a variety of studies that each will provide specific information, and with approximately 20,000 patients to be enrolled, this is the most ambitious proactive pharmacovigilance programme ever launched in Africa, for any drug. An independent Data Safety Monitoring Board will review the data - this data will be shared with national pharmacovigilance structures, as well as the Uppsala Monitoring Centre.

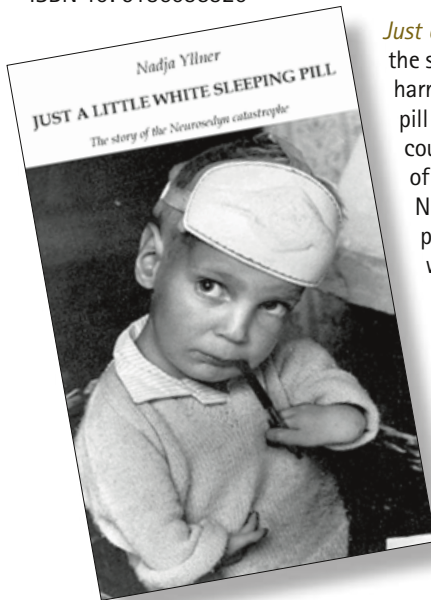
We fully concur with Dr Doodoo that pharmacovigilance is global and requires global support, especially in resource-constrained countries. We even more strongly support the notion that only rigorous scientific data on well-characterized products can serve to inform the pharmacovigilance community.

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*Dr. François Bompard, Sanofi Aventis, Paris, France (francois.bompard@sanofi-aventis.com)*

## The thalidomide story

276-page book published by Recito (info@recito.se)  
ISBN 10: 9186035320



*Just a little white sleeping pill* is the story about how a seemingly harmless little white sleeping pill by the name Neurosedyn could deform tens of thousands of children. The book follows Neurosedyn on its way from a pharmaceutical plant in post-war western Germany until this day. It portrays the mothers struggling for the right to keep their deformed children and the children's often traumatic childhood. We also meet those in power who made the fatal decisions. The attention around the Neurosedyn children led to a change in the way disabilities were seen. Children

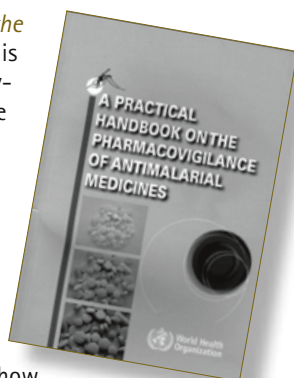
who had been hidden away in institutions were allowed into regular schools. The fear of a repeat of the tragedy changed the authorities' perspective on pharmaceuticals and patient safety. Thalidomide, the active ingredient in Neurosedyn, caused the worst pharmaceutical catastrophe in our time.

In her foreword Professor Barbro Westerholm writes "Congratulations to one of the most important books that has been written. It must be read by everyone responsible for us having access to safe and effective medicines, but also by others who estimates risks with chemicals and other things that we encounter in our environment".

The Swedish Thalidomide Society kindly donated a copy of the book to each national centre representative at the National Centres meeting in Uppsala.

## Anti-Malarials

This *Practical Handbook on the Pharmacovigilance of Anti-Malarials* is a detailed manual giving a step-by-step approach to the pharmacovigilance of anti-malarials. It is intended as a source of practical advice for pharmacovigilance centres. In addition, it provides details on how to conduct cohort event monitoring, the method of active safety surveillance for collecting information on all adverse events occurring after treatment. The manual also details how to perform causality assessment and signal identification. ISBN 978 92 4 154749 9 © WHO 2008



## Patient safety

We report belatedly on *Patient Safety* by Charles Vincent published by Churchill Livingstone/Elsevier. The book is aimed at all involved with healthcare, to explain the landscape of patient safety: how it evolved, research that underpins the area, key conceptual issues, action needed to reduce error and harm. The author comments "while I hope the book will be useful on the courses on patient safety... it is not a textbook. I have tried to write a clear, reasonably comprehensive overview of the major themes and topics".

The chapter titles are as follows:

- ◆ Medical harm: a brief history
- ◆ The evolution of patient safety
- ◆ Studies of errors and adverse events in healthcare: the nature and scale of the problem
- ◆ Reporting and learning systems
- ◆ Human error and systems thinking
- ◆ Understanding how things go wrong
- ◆ The aftermath: caring for patients harmed by treatment
- ◆ Supporting staff after serious incidents
- ◆ Culture and leadership for safety
- ◆ Making healthcare safer: clinical interventions
- ◆ Using information technology to reduce error
- ◆ People create safety

## Nepalese booklet

A booklet *Community Pharmacovigilance in Nepal* for community pharmacists has been published by the Regional Pharmacovigilance Centre at the Manipal Teaching Hospital in Pokhara, Western Nepal, in collaboration with Universiti Sains Malaysia, Penang. The booklet is a compact guide to pharmacovigilance in Nepal with answers about how to report ADRs. Mr Subish Palaian is the contact – subishpalaian@yahoo.co.in. (See article in UR42)

## Practice Guide

The 256-page *Good Pharmacovigilance Practice Guide*, published in November 2008 is a collaboration between different groups within the the UK's MHRA, (GPvP Inspectorate, the Pharmacovigilance Group and the Clinical Trials Unit). It relates to pharmacovigilance of medicinal products in human use and provides practical advice to key stakeholders, in particular Marketing Authorization Holders about achieving an appropriate system of pharmacovigilance. The paperback is published by Pharmaceutical Press: www.pharmpress.com.

## 2009 WHO meeting

The 32<sup>nd</sup> Annual Meeting of countries participating in the WHO Programme for International Drug Monitoring will take place in Rabat, Morocco on 2–5 November 2009, hosted by the Moroccan Centre of Pharmacovigilance.

## Try the Browser

Many users have been discovering improved efficiency and productivity through using the WHO Drug Dictionary Browser – which provides you on-line access to the WHO Drug Dictionary with a user-friendly interface.

The latest version of the WHO Drug Dictionary Browser allows users to filter search results, find generic and preferred names and browse both the latest version of the Dictionary as well as previous versions. CROs also have the possibility to select which Dictionary to browse depending on the demand of their sponsors.

If you have any questions regarding the WHO Drug Dictionary Browser or if you would like to apply for a one-week test account, please contact [drugdictionary@umc-products.com](mailto:drugdictionary@umc-products.com)

### The latest Drug Dictionary

The December 1 versions of the WHO Drug Dictionary Enhanced and WHO Drug Dictionary have been released. WHO Drug Dictionary Enhanced is also available integrated with WHO Herbal Dictionary (subscribers to this version have received an e-mail with login details.)

The Dictionary contains a large number of additional products – but there are no changes to existing entries with a few exceptions, the most important being that when an entry has been added which has the same name as an existing entry – but with other active ingredients; this results in a so-called non-unique name.

If you want to find out what has been added and which previously unique names that have been changed to non-unique in the B-2 format the Changes Files provide answers.

The latest statistics for the December 1 release are accessible via the [www.umc-products.com](http://www.umc-products.com) website. Documents there describe the number of unique names in all 94 countries, and illustrate the coverage of the countries where users conduct trials or market products.

### The 2009 dictionary

The next version of the Dictionaries will be released on March 1, 2009. In this version there will be a number of changes; products will be classified with the 2009 version of the ATC classification, and some products will be re-coded after quality control investigations.

### Prototype

From 2009 all development of the WHO Drug Dictionary Enhanced will be done through prototypes. Files with new features will be made available in parallel with the official Dictionary files. This will make it possible for companies and software vendors to prepare their systems and for the UMC to get feed-back to optimize the features and to produce guidelines for how to use the new features. The necessary changes will also be made in WHO Drug Dictionary.

The following prototypes will be available in 2009:

- A list of Drug Codes for all products that have an 'old form' flag in the C-format. This will make this useful feature available for B-2 format users
- A Generic preferred name level for multi-ingredient products
- ATC assignment on the 5th ATC level
- An extension of the Sequence Number 2 to four characters.

Detailed descriptions of these new features will be made available shortly.

### B-1 format to stop

Since 2002 there have been two versions of the B format: B-1 and B-2. They have the same structure but different inclusion criteria. The B-2 format is used for coding, but the B-1 format has sometimes been used as a reference – since it contained some company and country information. Since the WHO Drug Dictionary Browser was introduced the need for the B-1 format as a reference has been reduced, and will therefore not be distributed in 2009. The files will be available on request.

## Meet us in 2009

UMC staff will be available for discussion at the following:

- DIA CDM USA Marriott Market Street, Philadelphia, PA, USA, March 9-11
- DIA 21<sup>st</sup> Annual EuroMeeting Berlin 2009 Berlin, Germany, March 23-25

*continued from page 2*

Monitoring of public health programmes may be an area where the perfect is the enemy of the good, but no one with any sense will expose very large populations to new drug products without some 'reasonable' tolerance and safety testing. We need to be absolutely rigorous in risk management planning, and design studies that will answer reasonable concerns over safety and effectiveness balance, but not demoralise all of us by huge costs and complexity in seeking the fantasy of perfect observational safety studies.

Several times I have used the term 'reasonable' above, and this is a concept that challenges the whole of pharmacovigilance. What is the 'reasonable' benefit versus risk that we can accept for patients taking drug therapies?



# COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
9-13 February 2009	Excellence in Pharmacovigilance: Clinical Trials and Post Marketing	Paris, France	DIA Europe Tel: +41 61 225 51 51 Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org
11-12 February 2009	Data Safety Monitoring Boards	London, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org
23 February 2009	Periodic Safety Update Reports	London, UK	Management Forum Ltd Tel: +44 (0)1483 730071 Fax: +44 (0)1483 730008 www.management-forum.co.uk
4-5 March 2009	4th Annual Pharmacovigilance and Risk Management	Frankfurt, Germany	VIB events Tel: +44 (0)20 7753 4214 jocelynbenson@vibevents.com www.vibevents.com
9-11 March 2009	Advanced Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 730071 Fax: +44 (0)1483 730008 www.management-forum.co.uk
11/12 March 2009	Back to Basics in Pharmacovigilance	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org
23-25 March 2009	DIA 21st Annual Euro Meeting	Berlin, Germany	DIA European Branch Office Tel: +41 61 225 51 51 Fax: +41 61 225 51 52 E-mail: diaeurope@diaeurope.org
26 & 27 March 2009	Courses: Ecopharmacovigilance / Keeping the lights green - risk management roadmap / Basic Concepts in Pharmacovigilance	Verona, Italy	ISoP www.isoonline.org/
9-11 April 2009	P2T – including Journées de Pharmacovigilance	Marseille, France	Société Française de Pharmacologie et de Thérapeutique www.congres-p2t.fr/
25-27 April 2009	International Society for Pharmacoepidemiology (ISPE) 2009 Mid-Year Meeting	Stockholm, Sweden	ISPE www.pharmacoepi.org/meetings/midyear09/index.cfm E-mail: ISPE@paimgmt.com
25 May-5 June 2009	Pharmacovigilance - The Study of Adverse Drug Reactions and Related Problems	Uppsala, Sweden	the Uppsala Monitoring Centre Tel: +46 18 65 60 60 E-mail: info@who-umc.org www.who-umc.org
3-4 June 2009	Periodic Safety Update Reports (PSURs)	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org
8-10 July 2009	Medical Aspects of Adverse Drug Reactions	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org
12-15 July 2009	9th Congress of the EACPT	Edinburgh, Scotland	European Association for Clinical Pharmacology and Therapeutics (EACPT) www.eacpt2009.org/
4-8 August 2009	10th Commonwealth Pharmacists Association Conference	Accra, Ghana	CPA Accra 2009: E-mail: info@psgh.org www.psg.org/cpa
16-19 August 2009	25th Anniversary International Conference on Pharmacoepidemiology & Therapeutic Risk Management	Providence, Rhode Island, USA	ISPE www.pharmacoepi.org/meetings/25thconf/index.cfm E-mail: ISPE@paimgmt.com
6-9 October 2009	Annual Meeting of the International Society of Pharmacovigilance (ISoP)	Reims, France	ISoP www.isoonline.org/upcoming-meeting.html



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Uppsala Reports ISSN 1651-9779

