

# Uppsala Reports 35

**UPPSALA REPORTS October 2006**

For everyone concerned with the issues of pharmacovigilance

**ADRs from clinical trials**

**Reporting statistics**

**New publications reviewed**

**Pharmacovigilance and HIV/AIDS**

**The UMC responds to EU consultation**



# DIRECTOR'S MESSAGE



John Ruskin  
1819–1900

Summer vacations are not the time for being alert to drug safety matters, not for me at least. I want to read and think about philosophy and sail, and other stuff like that.

So I've been reading John Ruskin (1819–1900), the English critical thinker and philosopher. In his book, 'On Art and Life' (1853), he makes the much-quoted comment "You must either make a tool of the creature, or a man of him. You cannot make both." His point was in relation to Gothic architecture, where he claims that craftsmen had much more freedom to create decoration their way, under general direction only; whereas for Greco-Roman architecture, they were precisely instructed by the masters and had no individual freedom of expression.

Are we making people slaves of standard operating procedures, of standardisation, of rigid protocols, of regulation and audit and small-minded management? Even worse, censorship, delay, and even suppression of drug safety issues? I have come across instances of all the above, but the defence given is that the result will be in some way 'better'. I am not sure that is necessarily true. As Ruskin argues, whether Gothic or Roman architecture is 'better' depends, not on any standard, but on opinion. We have very few tested gold standards in pharmacovigilance, so let us leave enough real space for people to use their intuition and experience, and make truly original discoveries. I would venture that our major errors in drug safety have been due to not listening to people who find the first signals, rather than by failing to follow, for example, SOPs on case reporting.

The only matter of relevance to pharmacovigilance I saw in the international press over the summer was in relation to the war that was taking place in Lebanon. The WHO website ([www.who.int](http://www.who.int)) warns donors of drugs during major conflicts or disasters, to make sure their offerings are useful. Out-of-date products, labelled in a foreign language which is not likely to be understood by the recipients, or drugs irrelevant to the situation, simply make the chances of medical errors, during the pressures of humanitarian disasters, greater. Perhaps people should follow an SOP for drug donations? That would save valuable time and allow the workers on the ground to do more useful things!

A handwritten signature in black ink that reads "Ralph Edwards". The signature is written in a cursive style and is positioned above a horizontal line.

Ralph Edwards  
Director  
*the Uppsala Monitoring Centre*

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## Uzbekistan National Centre

In Uzbekistan our study of adverse drug reactions started in the 1970s, when the clinical pharmacology department of the Tashkent Medical Institute was directed by Professor K N Najmutdinov. In 1991, after the establishment of the pharmacological committee in the independent Republic of Uzbekistan, work on adverse drug reactions was taken on by this committee. Adverse reactions were monitored during clinical trials carried out for registration of medicinal preparations, as a result of which 15 foreign manufactured medicines were withdrawn from the registration process because of adverse reactions.



*A group working on adverse reactions in the Pharmacological Committee of Republic of Uzbekistan.*

*From left: Saidislom Abdullaev, Elena Doncheva, Baktiyor Shaislamov, Moisey Ayzikov.*

1998 saw further developments: M I Aizikov, the leading specialist of the pharmacological committee, participated in the training course 'Drug evaluation Efficacy and Safety' organized by WHO in Oslo. In mid-1998, Z S Salikhodjaev, deputy head of the pharmacological committee and M I Aizikov participated in a training course organized by WHO in Moscow. During both courses attention was paid to adverse reactions monitoring and activities of national centres in different countries. At the end of November 1998, by an order of the Ministry of Health, the commission on adverse drug reactions monitoring was created, bringing together leading scientists and specialists with an interest in this field. The commission monitored adverse drug reactions observed in clinical trials and routine medical practice. Under the guidance of Professor B Sh Shoislomov, the head of the pharmacological committee, an information appeal to the Republic's healthcare professionals was made and an adverse reaction card drawn up and sent to the heads of all healthcare bodies. The materials were published in three medical journals and in the newspapers. Under the heading 'About adverse drug reactions' two journals have carried regular articles on the question of drugs safety. The activities of the commission have led to withdrawal of several medicinal preparations (phenfluramine, terfenadine, the preparations containing erythrosine and tartrazine dyes, etc.); preparations containing phenylpropanolamine were included in the list of preparations for prescription-only. The commission has improved the methods of obtaining adverse reaction

reports from doctors and other specialists, participated in conferences on adverse drug reactions, and co-operated with foreign specialists. During this period the committee obtained more than 100 reports on adverse reactions of medicinal preparations.

In 2005 the First Uzbekistan National Congress on bioethics was held – where questions of medicine's safe use were discussed. E F Doncheva, the leading specialist of the Pharmacological committee, participated in Kishinev (Moldova) in the training course on adverse reactions (see UR30) with Sten Olsson (UMC) part of the faculty; he gave her valuable recommendations and samples of necessary documents. At the end of May 2005 as a result of the activities of the Pharmacological committee of Uzbekistan became an associate member of WHO Programme of International Drug Monitoring.

At the beginning of 2006, on the initiative of the Ministry of Health and active collaboration of Professor B Sh Shoislomov, the Head of the Pharmacological committee, and members of the commission in Tashkent and Samarkand, a training course for healthcare professionals, pharmacists and manufacturers was held entitled: 'Quality and safety of medicines – safety of a patient. Theory and practice of pharmacovigilance'. Materials were submitted by Sten Olsson, KILEN Institute (Sweden) and DrugInfo International (Moldova). As a result of the course a resolution on the creation of a specialized National Centre on adverse drug reactions was drawn up and accepted.

Thanks to the consultative and information help of the Uppsala Monitoring Centre, more than 20 adverse reactions reports were submitted during 2006 and the Republic of Uzbekistan became a full member of the WHO Programme.

## Uruguay update

the UMC has been advised of changes to the Uruguay pharmacovigilance system. The new main contact person for the National Centre in Uruguay is

**Dr Maria Cristina Alonzo**  
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We welcome Dr Alonzo as a representative in our world-wide network.

## Drop-box



Dr C Adithan, Co-ordinator of the Regional Pharmacovigilance Centre in Jipmer, Pondicherry has written to us about his unit's experience in collecting spontaneous ADR reports from their hospital. Previously, spontaneous ADR reports were collected when they met clinicians. To encourage further involvement in spontaneous ADR reporting, his centre has designed an ADR notification drop box and placed one in all important wards and out-patient departments. This has substantially increased the spontaneous reporting. The words on the front of the box read 'Reporting ADRs is part of our professional obligation - report all suspected ADRs'.



*The ADR drop box in use*

## Nigerian Merger

In June 2006, the National Agency for Food and Drug Administration and Control (NAFDAC) carried out a structural change for greater effectiveness of the pharmacovigilance programme. In this development, the Food and Drug Information Centre (FDIC) which hitherto carried out its operations from the laboratory complex of NAFDAC in Lagos under the Special Duties Division of the Agency, was merged with the National Pharmacovigilance Centre situated in the office of the Director General in the Federal Capital Territory, Abuja. Consequently, the Centre has changed its name to Pharmacovigilance/Food and Drug Information Center (PVG/FDIC).

This change was necessary to boost pharmacovigilance activities as well as to effectively co-ordinate the collection, analysis and dissemination of food and drug information. The new Centre is headed by Pharm (Mrs) A I Osakwe who reports directly to the Director General of NAFDAC, Prof Dora Akunyili. In another development, in July 2006 the Centre inaugurated its National Drug Safety Advisory Committee. These changes are expected to improve the impact of the pharmacovigilance programme in Nigeria in the near future.

## Sierra Leone Launch



*Top table at Sierra Leone launch: Mr H H Lawson, Miss Abator Thomas (Minister of Health and Sanitation), Dr Noah Conteh, Dr Sandy.*

The Registrar of the Pharmacy Board of Sierra Leone, Michael Lansana, has sent *the UMC* photos and press cuttings concerning the launch of the Pharmacovigilance Programme by the Pharmacy Board in Sierra Leone on 26th June 2006. A booklet has also been produced by the Pharmacy Board to coincide with the event, entitled 'A Guide for Detecting and Reporting Adverse Drug Reactions - Why Health Professionals Need to Act'. Wiltshire Johnson, Head of Drug Information and Pharmacovigilance attended *the UMC* course in 2005, and there has been steady progress in his country since then; it became an Associate Member of the WHO Programme in August 2005. Press reports of the event also spotlighted action by inspectors of the Pharmacy Board against substandard, counterfeit and illegal drugs, and the launch ceremony was followed by a public bonfire of confiscated drugs.

## Bright pharmacovigilance future in Tanzania

By Henry Irunde

### Background

Tanzania is an East African country with a population of roughly 36 millions; it has around 3,500 doctors, 10,000 nurses and 700 pharmacists. The country is a full member of the WHO International Drug Monitoring Programme and an ADR monitoring programme started formally in 1993. Healthcare providers are voluntarily requested to report spontaneous ADRs to Tanzania Food and Drugs Authority (TFDA) by using postage pre-paid reporting forms.

The TFDA is responsible for regulation of food, drugs, cosmetics, medical devices and related products in accordance with the Tanzania Food, Drugs and Cosmetics Act, 2003. According to this Act, TFDA is responsible for all matters related to use, quality, safety and effectiveness of medicinal products on the Tanzanian market.

### Need for the review

Since becoming part of the WHO Programme, the ADR reporting rate has been low. In 2002, zonal Drug Information Centres (DICs) were instituted at four referral hospitals (Muhimbili National Hospital in Dar Es Salaam, Mbeya Referral Hospital, Kilimanjaro Christian Medical Centre in Moshi and Bugando Medical Centre in Mwanza), but they failed to raise the level of ADR reporting activities.

TFDA requested a review of the current monitoring system, and this was carried out in July 2006 by Pia Caduff-Janosa from Swissmedic, Henry Irunde and Mary Masanja both from TFDA.

### Review objectives included:

- Review current procedures and processes for ADR monitoring, including training for health professionals and reporting form
- Conduct workshops on ADR reporting for health professionals at two hospitals that host zonal DICs
- Prepare a training manual for health professionals, TFDA and DIC staff
- Prepare Standard Operating Procedures (SOPs) for handling ADR reports
- Train TFDA and DIC staff on new procedures and on Vigibase Online
- Conduct meetings with stakeholders to discuss procedures for ADR reporting
- Issue recommendations to improve pharmacovigilance activities in Tanzania.

### Methodology

The approach included interviews with staff working in the TFDA pharmacovigilance section, the Director of Product Evaluation and Registration (DPER) and Director of Inspection and Surveillance (DIS). Along with viewing documents and data at the pharmacovigilance

section, a critique of available ADR guidelines and reporting form was also done, training materials for staff working at TFDA and zonal DICs were prepared, two zonal DICs were visited to train staff, and a stakeholders meeting conducted in Dar Es Salaam. The activity kept the project team busy for three weeks.

### Results

Widening the legal basis for manufacturers and holders of market authorization to report ADR and data management within TFDA is suggested. Four Standard Operating Procedures (SOPs) were drafted: signal detection at TFDA, ADR report processing at TFDA, ADR report processing at zonal DICs, and quality assurance of ADR reports at TFDA and zonal DICs.

Training on Principles of Pharmacovigilance, Good Pharmacovigilance Practice, Risk Assessment and Risk Management was conducted to both TFDA and DIC staff. Ten selected staff were trained in data entry and management on Vigibase Online.

The team visited two zonal DICs (Bugando and Kilimanjaro) and conducted seminars to healthcare staff – around 75 healthcare staff from each centre attended. A stakeholders meeting with 40 participants from drug manufacturers, academic institutions, consumers and medical doctors in charge of health facilities was organized at Land Mark Hotel in Dar Es Salaam.

### Areas of improvement

Current legislation doesn't provide for mandatory reporting of ADRs by Holders of Market Authorizations, so there is a need to amend the law to introduce mandatory reporting by industry. The two staff working in the pharmacovigilance section are also required to perform many other unrelated duties. This compounding of different tasks leaves them too few resources for pharmacovigilance duties such as collection and assessment of ADR reports, data evaluation, risk assessment, detection of new drug risks, risk communication and sensitization and training of healthcare professionals on drug safety. Their involvement in the review process of marketing authorization dossiers is of concern as this is incompatible with an unbiased approach to post-marketing surveillance. The same applies to pharmacovigilance staff working not in an independent unit but as part of the Directorate of Product Evaluation and Registration. A proposal to relieve staff of unrelated non-pharmacovigilance activities and to establish a separate unit is made, and the number of staff should be increased.

Spontaneous reporting is still very low (table 1) and ADR reports originate from doctors and pharmacists; no reports have come from nurses, consumers and industry (except Adverse Events from clinical trials). Vaccines are authorized by TFDA but monitored by EPI and there is no agreement for ADR monitoring between the two institutions; more collaboration with public health programmes is needed. Zonal DICs need to be reactivated by having a clear agreement between concerned parties regarding their respective responsibilities.



Figure 1: Map of Tanzania

The implementation of a new data management system via Vigibase Online should be a top priority as this will facilitate and speed up the detection of new risks related to drugs. Further long-term suggestions were to include pharmacovigilance training in undergraduate curricula, patient education, and to consider implementing ICH Guideline E2E on Pharmacovigilance Planning, at least for global companies who already submit Pharmacovigilance Plans in the ICH region.

Table: 1 Number of spontaneous ADR reports received per year 1991-2005

Year	Local products	Imported products	Total
1991			28
1992			9
1993			25
1994			17
1995			31
1996			62
1997			43
1998			8
1999			17
2000			40
2001			38
2002	9	108	117
2003/2004	4	56	63
2004/2005	1	78	79

## Implementation

In principle TFDA management has agreed to implement the recommendations, although this depends on human and financial resources. TFDA has vowed to establish a robust pharmacovigilance system geared towards protecting public health as well as achieving its vision of becoming the best regulatory authority in Africa by 2015. Our review has been done at a time when the Authority is trying to modernize and improve various systems and will add value to the existing pharmacovigilance system.



From left: Mary Masanja, Product Risk Analysis Officer - TFDA; M. Ndomondo-Sigonda, Director General-TFDA; Henry Irunde, Head Product Risk Analysis-TFDA and Dr Pia Caduff-Janosa from Switzerland

## Collaboration in Madagascar

Madagascar launched its national pharmacovigilance activities by hosting a five-day 'Training of Trainers' workshop from 19 to 23 June 2006. The workshop, organized by Madagascar's National Drug Agency (AMM, Agence du Médicament de Madagascar) and its Pharmacovigilance unit, was sponsored by the WHO country program office, USP (United States Pharmacopeia) and USAID (United States Agency for International Development). The training was facilitated by Professor Rachida Soulaymani Bencheikh, director of the Moroccan Anti-Poison and Pharmacovigilance Center, and her colleagues Dr Radja Benkirane and Dr Amina Tebaa. A total of 55 participants from different health care settings attended the workshop, representing all 22 regions of Madagascar. Madagascar is one of the first francophone countries in Africa to officially launch its national pharmacovigilance programme. The training of trainers took place only 4 months after a 2-day workshop was held which introduced the principles and importance of pharmacovigilance to representatives from Madagascar's health care sector. A few weeks after this 2-day meeting, the pharmacovigilance unit of Madagascar had not only developed its adverse event reporting form but was already testing this form in hospitals and health care centers in the capital, Antananarivo. Pharmacovigilance is gaining importance in most economically-challenged countries with the introduction of new drugs and/or combination drugs such as artemisinin based combination therapy (ACT) for the treatment of malaria.



The training group in Antananarivo

Madagascar's pharmacovigilance activities could not have advanced with such tremendous speed without the support of international partners, especially the collaboration with the Moroccan national centre, but essentially it is the passion and enthusiasm of Madagascar's National Drug Agency (under the direction of Dr Jean René Randriasamimanana) and Pharmacovigilance unit (Dr Donat Rakotomanana) with support from its Ministry of Health and Family Planning, which has anchored Madagascar in the global network of pharmacovigilance.

## Pharmacovigilance goes to the Caribbean

### WHO initiative

Barbados hosted a 'Training course for the Introduction of Pharmacovigilance into HIV/AIDS Programmes' from 11-16 September. The training was organized by WHO headquarters and the WHO Regional Office for the Americas/PAHO (Pan-American Health Organization) using funds provided by the European Commission and PAHO. Representatives of HIV/AIDS treatment programmes and drug regulatory authorities of 11 Caribbean countries were represented\*. None of the countries are currently involved in the WHO Programme for International Drug Monitoring, and some have a very small population.

### International faculty

The training programme included basic pharmacovigilance methodology introduced by Ralph Edwards and Sten Olsson from the UMC and Mary Couper and Marco Vittoria from WHO-HQ. Jens Lundgren from the University of Copenhagen provided participants with a comprehensive overview of the toxicities commonly associated with the three main classes of antiretroviral medicines (ARVs). He also introduced cohort-event monitoring systems that are established in various parts of the world and particularly the Euro-SIDA cohort that he is co-ordinating. A full day was devoted to discussions on how to manage HIV/AIDS patients affected by various drug toxicities.

### Focus on future actions

Participants were invited to interact with the lecturers and with each other during several working group sessions. They were also encouraged to create an action plan for how to proceed with the development of a pharmacovigilance programme for HIV/AIDS medicines in their respective countries. As the draft action plans were presented on the final day it became evident that all country representatives had bought into the idea of creating systems for the study of ARV toxicities. They presented plans for how this may be achieved that seemed realistic. It now remains to be seen if their plans will stand the test of reality and if they will be able to convince their health administrators and politicians that investing in wiser use of medicines with inherent toxicities ultimately benefits both individual patients and healthcare budgets.

WHO intends to follow-up the present course with more in-depth training in the Caribbean at a later stage.

\* Bahamas, Barbados, Belize, Dominican Republic, Guyana, Haiti, Jamaica, St. Lucia, St. Vincent & the Grenadines, Surinam, Trinidad & Tobago

*Photos from top:*

- 1. Nicole Felix, Saint Lucia speaking to the group*
- 2. Hector Balcacer, Dominican Republic, Naomi Jessurun, Suriname, and Robert Cazal-Gamelsy, Trinidad & Tobago in a lively group session*
- 3. Pleasant surroundings for a break-out discussion;*
- 4. Naomi Jessurun, Suriname, provides feed-back to Jens Lundgren and the group*





# WHO assignment in Botswana

*David Coulter*

It was an enjoyable and a productive time as we met together in the Ministry of Health in the capital, Gaborone, to plan for pharmacovigilance in Botswana. The participants were the whole of the Drug Regulatory Unit – ten pharmacists led by Dr Selelo. Dr Shanthi Pal from WHO Headquarters and I were the tutors, but we gained a lot from the local team. We learned about Botswana, its people, their needs and the way pharmacovigilance principles could be adapted to meet them.

Botswana, a land-locked country which borders on South Africa, Namibia and Zimbabwe is an independent republic with a small population of 1.68 million. At the end of September they celebrated 40 years of independence and have made great progress politically and economically. Most of the country is desert – the famous Kalahari. Botswana is also famous for its wildlife, both land animals and avian. Water is the most important commodity; their currency is called the Pula, the word for water. The predominant colour on their flag is blue, also representing water.

HIV/AIDS is the main public health problem, along with tuberculosis. Malaria is present in some areas, and pneumonia and diarrhoeal diseases are common in small children. URTI, urinary tract infections, skin diseases, hypertension, diabetes, and cardiovascular disease are also common. WHO-sponsored public health programmes are being undertaken for HIV/AIDS, malaria, childhood immunisation and tuberculosis. It is therefore easy to see that medicines are extremely important in individual care and public health. Pharmaceuticals comprise 62% of the Health Budget and good pharmacovigilance will be very important in providing optimal patient care, achieving successful public health programmes and getting the best value for this money.



*David Coulter (far left), with Drug Regulatory Unit staff and Shanthi Pal.*

The first PowerPoint slide I showed was the flag of Botswana and the group agreed to sing their National Anthem. I didn't understand the words, but they sang beautifully and the anthem was impressive. This seemed to set the tone for the whole course because pharmacovigilance is about helping their people; it is not an academic exercise.



*The Ministry of Health building, Gaborone.*

The full week's course in September covered the field in basic pharmacovigilance subjects. Participants also received hands-on training in Vigiflow (Vigibase Online) and Vigisearch. Working groups designed a national reporting form. There was great rejoicing when this was finally agreed. There were exercises in causality assessment. Participants also planned the implementation of pharmacovigilance. An important part of this will be to liaise with the public health programmes. Consideration was also given to a cohort event monitoring study on a few medicines (eg ARVs) in the immediate future as a means of stimulating interest and getting good data on medicines important locally.

The group had done a lot of prior thinking and there was much intelligent discussion. This input was a major factor in a successful outcome rated highly by the participants. Like us, they would have liked a few more days.

## UMC thoughts on EU pharmacovigilance

*The European Commission commissioned the Fraunhofer Institute for Systems and Innovation Research to make a comprehensive assessment of the EU system of pharmacovigilance at a European and Member State level, and make recommendations to increase its robustness. In July, the UMC issued a response to the public consultation on the Fraunhofer Institute Report (FIR).*

### General

*the UMC* argues strongly that considering drug safety as primarily regulatory and epidemiological is too limited, and that the gaze of pharmacovigilance must be focussed on the needs of individual patients and their health professionals. This is not only a serious philosophical point, as there is movement towards 'individualised health care' and genomics which will influence the way in which we view drug therapies in future.

### The current situation

The concentration on regulation and standardisation in the west, particularly ICH-related, is reflected in the EU. This has been valuable in bringing industry and regulators together, such as standardised ADR reporting forms, periodic safety update reports and risk management guidelines. EMEA has also developed the Eudravigilance system for storage and transmission of reports. This duplicates much of what WHO does, but there is provision for the WHO database to receive EMEA reports and vice versa. The WHO database receives all suspected ADR reports from national centres, not only those that are 'unlabelled' and serious. Older drugs are amongst the top ten drugs reported to the WHO database, which has major implications for patient safety and drug therapy.

### Data sources and safety issue detection

*the UMC* wishes to discuss and understand the EU's future requirements in medical terminologies, and correctly represent those needs in its work in the technical support of the WHO Family of International Classifications (WHO-FIC) Network. The WHO/UMC uses important internationally accepted tools to support its work in pharmacovigilance and would like to collaborate fully with the EU in making the best use of them.

*the UMC's* Drug Dictionary database linking medicinal products with their ingredients, has each product classified according to the WHO ATC classification, is updated continuously, and fully controlled versions issued quarterly; collaboration with IMS Health ensures global coverage of data. Offering the ingredients data with unique identifiers to the ICH free of charge, including maintenance, might further the EU's work.

*the UMC* has an advanced, automated duplication detection system and combined efforts on quality assurance should prove beneficial. Efforts should be made to ensure that data in the Eudravigilance and EU national databases are totally and accurately reflected in the WHO Database.

### New legal tools

The legal framework for regulators and industry should be shifted to more productive areas for safety. Industry always faces the legal consequences of negligence and failure to warn, so it seems logical

that the PSUR summary findings should be represented in product information changes accurately. The regulator's responsibility could be limited to making sure that happens and that PSURs are produced as agreed. Instead of legislation on the time transmit of ADR reports, there could be agreed quality assurance of the whole process from receipt of a report to action taken, and impact analysis.

### Decision-making

*the UMC* would like to work with the EU to develop guidelines for decision-making processes and data collection triage and analyses that must support the decisions, based on the principles of the Erice Declaration and CIOMS work. The key decision-making steps are:

1. What signals to evaluate further.
2. What specific kind of studies would be most helpful in taking selected signals further.
3. How to communicate potentially serious but incompletely investigated signals.
4. Determining the impact of new information on the relative effectiveness and risk of therapies for a particular clinical indication.
5. How to communicate the results of the analysis in 2.

A major goal should be to have true transparency: the need for care in managing a signal in order not to cause a 'drug scare' is recognised, but the public is not served by silence over evolving safety issues either. Two critical issues over decisions about drug safety are typified by the 'Vioxx case'. The first relates to the time which elapses from the first signal to a 'definitive' decision; the second issue is that decisions about one drug affect the use of others, and there is too little information about a range of reasonable courses of action for health professionals.

### Impact of communications and actions

*the UMC* runs a confidential e-mail distribution list for discussion of drug safety issues: Vigimed. We propose that this be used more actively by the developed country regulators. Existing networks between regulatory authorities (eg USA, Canada, Australia, Sweden) could be expanded, and there is perhaps a place for regional networks, reflecting different public health needs.

Developing countries complain that they are caught unawares when a developed country's decision on drug safety is published in the press before they know about it. Many countries including EMEA are very good at informing the WHO/UMC about decisions they have made, but the notice time is too short for regulators to react responsibly. Difficulties arise when decisions in one regulatory body conflicts with another.

### Monitoring compliance and quality management

The WHO/UMC seeks to understand how it may co-operate better with the EU in their pharmacovigilance work, and jointly how the EC and *the UMC* may foster global harmonization and development in the safety of medicinal products. The WHO, having taken the lead over many health care standards (terminologies/ dictionaries/classifications and definitions), offers all its knowledge, data and analysis to participating countries in the WHO Programme. In this

respect EMEA has always been regarded as a 'national centre', and had access to the same services as individual EU countries.

### Other comments

The response finally notes the impact decisions and activities in one country have on others, particularly the 'developed' world on the 'developing'. EU and other developed countries' policies are often impossible to follow for resource poor countries, even when the developments themselves are desirable. Countries with limited resources are destined to have not only the heavier burden of disease,

and limited health care resources, but also suffer from not being able to develop regulatory and drug safety systems in an optimal way. EU support for the delivery of needed and requested tools for drug safety to member states of the WHO Programme would be welcome.

*The 11-page referenced response is available from the UMC website – it represents the views of the Director and senior staff at the UMC. The opinions are not necessarily the official view of the WHO.*

# New work begins at Erice

*Nine years after the Erice Declaration, an important new document will soon be published*

### *Bruce Hugman reports from Sicily*

A decade after the meetings which resulted in the creation of the influential Erice Declaration, a new international group of experts met in July this year in the ancient mountain-top city of Erice, once more convened by Professor Giampaolo Velo of the University of Verona. Their task was to examine the current state of pharmacovigilance and to map out how it could be developed and strengthened in the future, particularly with regard to making a more direct contribution to the broader objectives of the patient safety movement.

Debate focused on a number of core issues:

- Strengthening and broadening the theoretical base and practical impact of pharmacovigilance
- Embracing the patient-focused values of the patient safety movement
- The reduction of bureaucracy in pharmaceutical safety
- Maximising existing data sources and seeking new ones
- Transparency and trust
- The contribution of supranational organisations
- The long-term future of pharmacogenetics in pharmacovigilance
- Priorities and challenges in emerging countries

There was agreement that, after many years of considerable achievement, fundamental reassessment of the science was required if it were to be fit for purpose into the future and was to serve the varying and demanding priorities and contemporary needs across the world.

Twenty-seven experts from twelve countries were brought together at the Ettore Majorana Centre for Scientific Culture, under the auspices of the International School of Pharmacology. The participants represented regulators, clinicians, academics and researchers, pharmacovigilance specialists, the pharmaceutical industry, private and international organisations and communications specialists.

The discussions resulted in a dense and challenging agenda for reform which will be published soon as a radical new Erice document. The latest drafts are currently being scrutinised by the participants, prior to publication and worldwide consultation in due course.



*Participants in the meeting take time off in Segesta, one of the finest ancient sites on the island of Sicily, with its magnificent Doric temple [inset].  
Thierry Trenque, Giampaolo Velo, June Raine, Abida Haq, Judith Jones.*

## Management of Adverse Drug Reactions arising from Clinical Trials

### A summary of responses from national drug regulatory authorities

*Ushma Mehta, member of the Pharmacovigilance Committee, Medicines Control Council, South Africa*



*Ushma Mehta*

Assessing the safety and tolerability profile of investigational new drugs (INDs) is an essential objective of pre-marketing clinical trials. In response to recent concerns about the quality of safety reporting from clinical trials the principles of good pharmacovigilance practice have been integrated into the earlier phases of drug development. This has given rise to improved clinical trial safety monitoring and a more pro-active approach to signal detection and risk assessment. These changes highlight the importance of building capacity within drug

regulatory authorities to manage, assess and respond to safety information received from clinical trials, pharmacoepidemiology studies and meta-analyses of safety data.

The responsibility for monitoring the safety of study subjects during clinical trials is shared between researchers, ethics committees, trial sponsors, clinical trial monitors and drug regulators. Drug regulatory authorities have the unique responsibility of ensuring that these INDs are relatively safe, effective and of good quality prior to being allowed for use by the local population. They also have the responsibility of ensuring that these products are safe for use in local study subjects. Guidance documents such as the good clinical practice (GCP) guidelines and International Conference on Harmonization (ICH) guidelines on the expedited reporting of clinical safety data have done much to improve and standardise safety monitoring and reporting by researchers and sponsors during clinical trials. ICH guidelines require that only serious unexpected suspected adverse drug reactions (SUSARS) are reported in an expedited manner to regulatory authorities. However, there is no guidance on whether and how non-serious or expected adverse reactions should be reviewed by regulators. In fact, these guidelines do little to provide regulatory authorities with procedures on how to manage and respond to such information.

Clinical trial ADRs are somewhat different to spontaneously reported post-marketing ADRs in ways that could affect the way they are handled by regulators:

- During clinical trials adverse events are often solicited and actively monitored.
- Causality assessment of individual events may not necessarily be conducted by clinical investigators for individual reports, particularly when the investigators are blinded to study medication use.

- A single IND may be tested simultaneously for different conditions, by different investigators, at different doses and in different populations, locally and internationally at the same time.
- Clinical trial ADRs are often reported as blinded so the identity of the suspected drug is not known at the time of the reaction. Reports are usually only unblinded when essential for managing the patient experiencing the ADR.
- The population exposed to the IND is known, reasonably well-described and usually followed up over a period of time. Therefore follow-up and outcome data is usually available for patients who have experienced an adverse event.
- Differences in the incidence of adverse events between comparative treatment arms are used to statistically assess the strength of association between events and new drugs or regimens.

In order to determine how the above differences are addressed by regulatory authorities, an e-mail was sent out on Vigimed on behalf of the South African medicines regulatory authority in June 2006. This e-mail asked four questions relating to the management and review of ADRs reported from clinical trials involving INDs. Six, very useful responses were received and are summarised in the table below. A review of the procedures for managing clinical trial ADRs suggests that the procedures for handling IND clinical trial ADRs are very different between countries.



*Clinical trials in the news*

Of the six countries that responded, all except one entered the ADRs into a centralised database. Three of the respondents entered the IND-related ADRs into their post-marketing spontaneous reporting database, however in order to do so additional fields are included for IND-related ADRs. The EudraVigilance database, which houses pharmacovigilance data from member states in the European Union, has separate modules for pre- and post-marketing ADRs and also collects international ADRs. In Malaysia and Canada a totally different database has been

developed for clinical trial ADRs. However, in Malaysia, these reports are transferred into the post-marketing database once the product is licensed.

Belarus, Canada and Tunisia enter both blinded and unblinded events into the database. However in Canada, once the blind is broken, the information is updated in the database to reflect the new information. Only Ireland reports entering both serious and non-serious adverse reactions into the database and only Canada

Question	Belarus	Canada	Ireland	Malaysia	Serbia	Tunisia
Are adverse events from IND trials collected and entered into a central database?	Yes	Yes	EudraVigilance for EU member states	Yes	Yes collected but no database	Yes
Is this the same database as that used for spontaneous reports?	Yes but different fields	No Under clinical trials division	Yes but different fields EudraVigilance database – separate modules	No Under clinical trial division	No database Only have database for spontaneous reports	Yes
Are both unblinded and blinded reports entered or just unblinded reports?	Both	Both Unblinded reports updated	Unblinded	Unblinded	Unblinded	Both
Are only serious ADRs entered or all?	Serious	Serious unexpected	All	Serious	N/A	Serious
Are only local reports entered or foreign reports as well?	Local (international data - separate analysis)	All	Local (EudraVigilance – for international data)	Local	N/A	Local
What is the review process for these ADRs?	Analysis of summary reports and where needed DSMB reports	Multidisciplinary Clinical trial safety review team. Triage and daily review of reports	Individual and cumulative review by trial, reaction, drug etc. Annual safety reports and DSMB reports	Summary report tabled at drug review meetings	Follow-up when necessary. Assess causality & monitor the rate of SUSARs from local and international sites	Periodic analysis. Liaise with ethics committee and investigators for follow-up of local reports
Is this part of post-marketing pharmacovigilance system?	PCV Unit	Clinical trial unit	PCV centre	Clinical trials unit	PCV centre	PCV centre

enters international reports as well as local ones. In the case of investigator-initiated studies (ie not sponsor-initiated), the Irish Medicines Board submits these reports to EudraVigilance, while sponsor-initiated study reports are submitted to EudraVigilance directly by the study sponsor.

In all six countries, some kind of review process for these reports occurs. All except one country describe a procedure to assess the causality of individual locally-reported events while all respondents reported a periodic or ad-hoc review of cumulative data, including annual summary reports and data safety monitoring boards' results. Tunisia and Belarus specifically mention their contact with ethics committees and investigators. In addition, inspections of clinical trial sites are conducted periodically to ensure that the trials are being conducted in accordance with the principles of Good Clinical Practice (GCP).

Based on the information provided, the following elements (in no order of priority) of an IND clinical trials regulatory pharmacovigilance system appear to be necessary:

- 1) Data collection that facilitates the assessment of locally-reported ADRs by product, protocol, reaction type and, if possible, study site. At a minimum these should include serious, unexpected suspected adverse reactions (SUSARs).
- 2) Periodic and ad-hoc review (even in summary form) of up-to-date safety data of the IND based on local and international reports of serious and non-serious reactions; DSMB reports as well as any special safety studies.
- 3) Legislation enabling the following regulatory decisions to be made:

- a. Revising the Clinical Trial Protocol, the Informed Consent Form and the Investigator's Brochure
  - b. Informing investigators, study participants (and where necessary the public) of any new safety concerns identified, particularly when crises arise.
  - c. Suspension of the trial for further investigation of new safety signals
  - d. The termination of the trial.
- 4) Procedure to incorporate the safety information obtained from the clinical trials into the licensing review process and post-marketing use.
  - 5) Communication procedures that allow the regulator to liaise with local ethics committees, sponsors and investigators, particularly where ethical or safety concerns require further investigation.
  - 6) Inspection procedures for trial sites to ensure that local clinical trials are conducted in accordance with approved GCP guidelines.

The way in which regulatory authorities achieve these depends largely on the local regulatory infrastructure, available resources (human, technical and administrative) as well as extent to which clinical trials are being conducted locally.

## Acknowledgements

*Sincere thanks to Svetlana Setkina, Hoda Eid, Clodagh Brennock, Abida Syed M Haq, Milena Mijlkovic, Chalbi Belkahia and Sihem El Aidli for their useful responses that facilitated the synthesis of this report.*

## Which comes first...?

by *Sten Olsson*

### An old question re-visited

An interesting e-mail from Dr Parvana Shafiyeva, at the Ministry of Health of Azerbaijan Republic led us back to the old question: "which comes first, pharmacovigilance or regulation?".

She is embarking on the long process of creating a comprehensive pharmaceutical management system for Azerbaijan with a revamped registration process. She refers to the fact that Azerbaijan has a lot of non-registered medicines on its market and she simply asked "How necessary is it to begin the pharmacovigilance activity now, when the registration procedures are not so well developed?".

### The traditional approach

The traditional way of building a comprehensive national system for medicines supply and rational use of medicines is to start from the basis of medicines policy and legislation. According to this approach politicians first have to decide what the national medicines policy should be and how the administrative structures should be designed. This is then set out in legislation decided upon by the national legislative body, normally the parliament.

### Legislative preparations

On the basis of this legislation, regulatory agencies develop detailed regulations for drug registration, distribution, manufacture, wholesale, retail, quality control etc. Very often the rules concerning safety monitoring come last in the chain of regulations and processes, which is not optimal from a public health viewpoint. The procedure of deciding policies and regulations and establishing effective processes is very time-consuming. While these procedures are going on you really do not know the extent of drug-related problems in society and which problems are the most serious ones. A significant number of non-registered products on the market is in itself a risk – knowledge of the way the unregulated market causes health problems is essential.

### Another way?

The alternative, problem-based, approach is to start by setting up a system for reporting of problems related to drug therapy. By advocating this reporting system widely and involving both health professionals at all levels of health care and patients themselves you can quickly get a reasonable picture of the most pressing health issues which are related to the use of medicines. Then you can identify in which areas laws, regulations and quality assurance processes are most urgent. Setting up a pharmacovigilance system at an early stage thus facilitates priority setting when working out a comprehensive drug management system for a country.

## FIP recommendations

The Working Group on Public Policy of the International Pharmaceutical Federation, FIP issued a statement of policy on the 'Role of the Pharmacist in Pharmacovigilance' at its 66th Annual Congress in Salvador Bahia, Brazil<sup>1</sup>. The statement makes recommendations effecting the training of pharmacists, the involvement of practitioners, and the responsibility of medicine control agencies to provide resources, compensation incentives and systems that will enable the pharmacist to achieve maximum benefit from their efforts.

The FIP Statement of Policy 'The Role of the Pharmacist in the Prevention and Treatment of Chronic Disease' was approved at the FIP congress in Brazil and is now downloadable from the FIP website: <http://www.fip.org/www2/> (see page 16).

<sup>1</sup> *International Pharmacy Journal*, 2006, 20:1.

## ISO progress update

*Marie Lindquist reports*

The International Organization for Standardization meeting in Geneva, Switzerland, in early October continued its consideration of matters relevant to pharmacovigilance.

WHO/UMC are now formal members of the ISO Working Group 6, and have the right to vote on proposed standards. ICH and CDISC (Clinical Data Interchange Standards Consortium) have also applied for liaison status, and await approval.

The work items that have a bearing on the WHO Programme have progressed, but not to a voting point. More input is needed, particularly to the two items that deal with medicinal product identification.

One technical committee is discussing the business requirements for an International Coding System for Medicinal Products. The argument is that an international coding system for medicinal products is needed, and should be created.

It has been proposed that the ISO standard for electronic reporting would be ICH E2B with additions. Issues concerning ICH guidelines, HL7 ICSR and how to relate with the WHO Collaborating Centre remain to be discussed.

## WHO website

The section of the WHO HQ website devoted to pharmacovigilance was recently revamped, and is a useful source of information; there is more than appears from first entry via:

[http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/en/](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/en/) in the four sub-sections:

- Safety
- Efficacy
- Utilization
- Publications

## Reflections on the development of pharmacovigilance

Every quarter, Ralph Edwards, Director of *the* Uppsala Monitoring Centre offers his thoughts on the progress of pharmacovigilance, the WHO Programme for International Drug Monitoring and the safety of medicines in general. These are published in each issue of Uppsala Reports (UR) and on *the* UMC's website.



Ralph in his office

We have now gathered together his 'Director's Messages' and made them available for download (as a pdf file) from *the* UMC website (Home > Director's Message, foot of page).

The seventeen commentaries range widely from meetings to Vioxx, transparency to signals, and we hope you find them stimulating.

## Questions frequently asked

The collection of Frequently Asked Questions on *the* UMC website is also gradually being updated and added to; it currently covers:

- The WHO Adverse Reactions Database - Basic Facts (a 9-page Adobe Acrobat document giving basic background information)
- ICD (International Classification of Diseases)
- Anatomical Therapeutic Chemical classification
- Access to the WHO database
- Vigimed
- Abbreviations used in pharmacovigilance (an Adobe Acrobat file)

## UMC in print

### Nomenclature of herbals

*the* UMC research on accepted scientific names for therapeutic herbs is now published.

Farah MH, Olsson S, Bate J, Lindquist M, Edwards R, Simmonds MSJ, Leon C, de Boer HJ, Thulin M. Botanical Nomenclature in Pharmacovigilance and a Recommendation for Standardisation. *Drug Safety*, 2006, 29 (10):1.

This paper sets out the theory and research behind Dr Farah's recent work on accepted scientific names for plants used in medicine, and the benefits for drug safety work at *the* UMC.

### A round-up of recent papers and articles involving UMC staff

Savage, R. L. and A. Kiuru (2005). Thiazolidinediones and lowered HDL cholesterol. *Diabetes Care* 28(9): 2329-30.

Hugman, B. (2006). The Erice declaration: the critical role of communication in drug safety. *Drug Saf.* 2006; 29(1):91-3.

Hugman, B., Edwards, I. R. (2006). The challenge of effectively communicating patient safety information. *Expert Opin Drug Saf.* 2006 Jul; 5(4):495-9.

Clark D. W., Strandell J. (2006). Myopathy including polymyositis: a likely class adverse effect of proton pump inhibitors? *Eur J Clin Pharmacol.* 2006 Jun; 62(6):473-9. Epub 2006 Apr 22.

Bate A., Edwards I. R. (2006). Data mining in spontaneous reports. *Basic Clin Pharmacol Toxicol.* 2006 Mar; 98(3):324-30.

Edwards I. R. (2006). What is drug safety? Celebrating 20 years of the Drug Safety journal. *Drug Saf.* 2006; 29(6):461-5.

Handoko K. B., Souverein P. C., van Staa T. P., Meyboom R. H., Leufkens H. G., Egberts T. C., van den Bemt P. M. (2006) Risk of aplastic anemia in patients using antiepileptic drugs. *Epilepsia.* 2006 Jul; 47(7):1232-6.

Olsson S., Pal S. Drug bulletins: independent information for global use. *Lancet.* 2006 Sep 9; 368 (9539): 903-4.

## UMC Staff Farewells

We have sadly said goodbye to Erik Swahn, Linda Wallin and Malin Ståhl, who all left *the* UMC during the summer.

Malin, who has been an important member of the team at *the* UMC since 1998, has decided to begin studies in medicine, and we wish her every success in that, and to all three for the future.

## UMC at DIA

*the* UMC was well represented at the 42nd Annual Meeting of the Drug Information Association in Philadelphia, USA in mid-June. Staff from Products and Services had an exhibition stand with an array of materials about the services of the Centre and presentations took place in the lecture halls.

Marie Lindquist, spoke on 'Vigibase – a Global Resource for Patient Safety'. As well as describing in considerable detail the technical means by which *the* UMC achieves its work in collaboration with national pharmacovigilance centres, she stressed the goal of all drug safety programmes – the safety of patients. Underlining the methods of data access available for the WHO Programme and external organisations she declared that the strengths of the WHO database (Vigibase) – continuous data collection, low cost, size of data-set (>3,600,000 individual case safety reports), possibility to make country comparisons and analyse differences between countries/regions, E2b compatibility and quality management systems, out-weighed under-reporting and missing data, both of which can now be dealt with by BCPNN.

In 'Knowledge Finding: Data Mining in Patient Record Data', Andrew Bate gave the background of routine data mining at *the* UMC since 1995, described the application of BCPNN data mining methodology to patient records, and discussed the types of valuable information that can be captured by routine data mining of a longitudinal data set. He demonstrated that *the* UMC's methods have the potential to highlight signals early.

In a recent project with the IMS Disease Analyzer examining trends in the UK primary care database (computerised clinical records maintained by general practitioners) the benefits and limitations of data mining patient records versus formal studies were compared. The speed of conclusions, flexibility, freedom from prior hypothesis – discovering the previously unexpected, alongside use as active surveillance, potential for complex pattern recognition, were significant. Signals can be found using data mining in this data set. The limitations are that the method is not testing a hypothesis and data capture is not optimised for run of interest. Better understanding of the data will allow further method refinement in future. Hypothesis testing is still needed, however.

## Pharmacists' society continues training in patient safety

Pharmacists around the world have a major role in detecting, reporting and preventing drug-related problems. The International Pharmaceutical Federation, FIP, fully accepts this professional task of pharmacists and wishes to contribute to the training of its members by offering a training course on 'Pharmacovigilance and Patient Safety' in connection with its annual conference.

This year this conference was held in Salvador, Bahia, Brazil. The pre-conference training course was carried out 25-26 August. About 25 participants from around the globe took part in this training. Building on experience from the first training course held in Cairo last year (see UR31), lectures and working group discussions focused on some key messages:

- Definitions of key concepts and the need for pharmacovigilance
- Reporting systems and importance for patient safety
- Setting up and running a pharmacovigilance centre
- Identifying and analyzing drug safety signals
- Communicating with health professionals, media and the community.

Responsible for the different sessions were Carlos Vidotti (Brazil), Graeme Vernon (Australia), Sten Olsson (Sweden), Andy Grey (South Africa) and Alex Dodoo (Ghana).



*Sten Olsson, Alex Dodoo, Fred Koning (the founder of Lareb in the Netherlands) and Murilo Freita Dos, Head of ANVISA, the Brazilian National Pharmacovigilance Centre, at the FIP training event*

The technical working group on pharmacovigilance, recently created by Pan American Network for the Drug Regulatory Harmonization (PANDRH) took part in the deliberations of the FIP seminar, giving it an added relevance for the American continent

## UMC visits CEATOX

In mid 1990s, before Brazil had a national pharmacovigilance system, *the* UMC started collaborating with the Regional Poison and Pharmacovigilance Reference Centre in São Paulo (CEATOX). The centre, now located in Dr Odilo Antunes Siqueira Paediatrics



*At the CEATOX offices: Cristina Andrusaitis Sandron, Marcia de Almeida, Sten Olsson, Fernanda Ayache Nishi, Anthony Wong, Eliane Gil Rodrigues de Castro.*



Hospital, is directed by Dr Anthony Wong. The collaboration with the CEATOX reference centre has continued also after the establishment of the national centre at the regulatory agency ANVISA in Brasilia and the São Paulo regional centre continues to submit adverse reaction case reports to the WHO database.

In connection with his participation in the FIP pharmacovigilance seminar in Brazil (see above) Sten Olsson from *the UMC* was invited by CEATOX to give a presentation at the paediatrics hospital in São Paulo about international pharmacovigilance and the role of healthcare practitioners in identifying drug-related problems. In addition to giving his talk Sten Olsson had the chance of interacting with the CEATOX staff and learning about the daily operations of a busy poison information centre.

## Costa Rican course

A 'Basic Course in Pharmacovigilance' was held in the Centro de Desarrollo Estratégico e Información en Salud y Seguridad Social (CENDEISSS) in San José, Costa Rica, from 25th to 27th September 2006. There were 38 participants, who were all professionals (pharmacists) working in the Caja Costarricense de Seguro Social (C.C.S.S). All participants expressed their interest in contributing in this field from their working places in the different health centres across the country.

Dr. Astrid Alvarado Chaves and Dr. Erika Unfried, Pharmacist at the Drug Information Centre (Pharmacist Service) at San Juan de Dios Hospital coordinated the organization of the training course. Dr Unfried taught all the course, including materials provided from *the UMC*.



*Course participants inside the CENDEISSS building with Dr Unfried in the centre front.*

## Pharmacovigilance in the Horn of Africa

The Horn of Africa Network for Monitoring Anti-malarial Treatment (HANMATT) held a 5-day pharmacovigilance and quality assurance workshop in Alexandria, Egypt from 16th to 20th September 2006.



*Participants and facilitators at the HANMATT pharmacovigilance workshop.*

Participants included programme managers and experts in malaria from Somalia, South Sudan, Sudan, Yemen and Ethiopia with facilitators from WHO (African Regional Office, Eastern Mediterranean Regional Office, Headquarters) and CDC (Centers for Disease Control and Prevention) Atlanta, USA. Dr Abdelkrim Smine (United States Pharmacopeia Drug Quality and Information (USP DQI) Program) led the presentations on drug quality assurance with Dr Alex Dodoo (University of Ghana) handling the pharmacovigilance workshop. Dr Michael Green described methods for colorimetric assessment of product quality whilst Dr Andrea Bosman (Roll Back Malaria) gave a briefing on ACT (artemisinin-based combination therapy) implementation and also thanked the organisers and participants for a fruitful workshop.

## Reporting to the WHO database

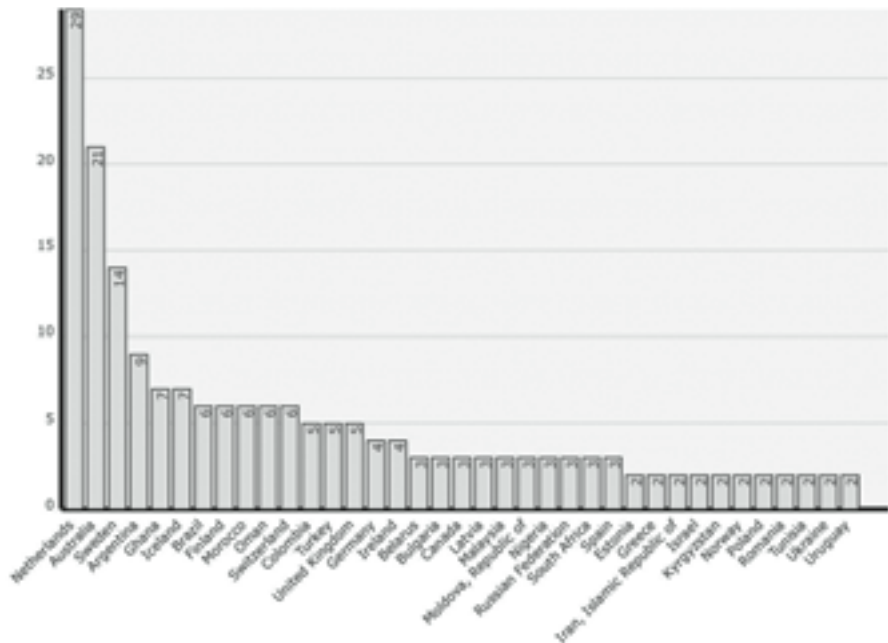
The WHO Programme for International Drug Monitoring is constantly expanding. New full members of the WHO Programme during 2006 are Belarus, Uzbekistan and Nepal, and there are several associate countries that we are supporting in the final stages of completing their 20 test cases to be accepted as full members. A consequence of this expansion is a large amount of ADR reports that has to be added to Vigibase at the moment, with the input team working hard to catch up after the Swedish summer vacation. Recently all the USA reports corresponding to the last two quarters of 2005 have been processed (around 120,000 reports in total).

When processing a batch of reports\* the goal is that at least 75% of the cases should be correct, ie that they should be active in Vigibase after the processing. Most often this means plenty of pre-processing work (including coding of medicinal products, mapping of ADR terms and correction of the format), which is performed before the ADR reports are ready to be added to Vigibase. As of the 4th of September 2006 the total number of correct and active ADR case reports was 3,760,836.

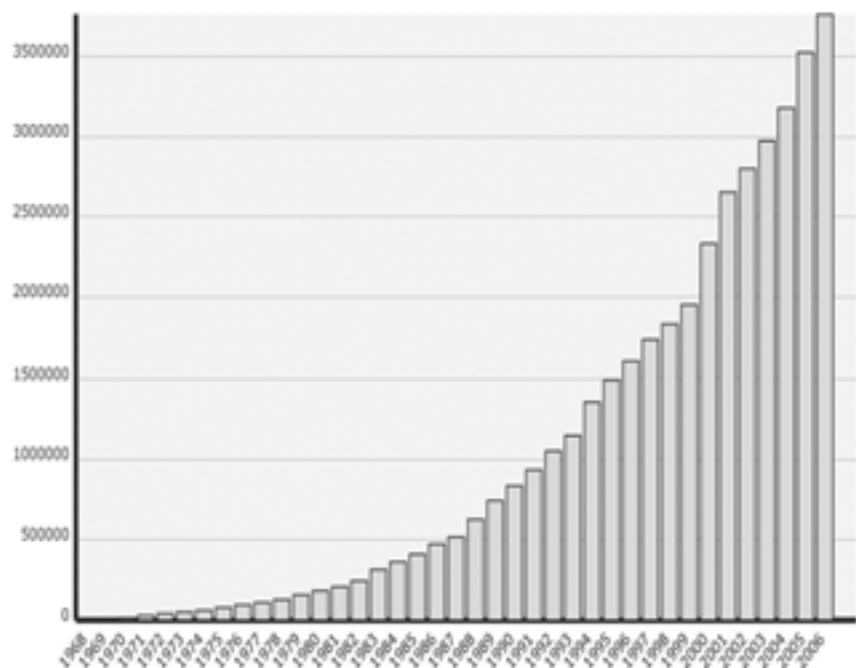
the UMC's Safety Reporting Support and Service team have supplied the following data on submission of adverse drug reaction reports to the WHO database (Vigibase) in Uppsala.

### Country submissions

Graph 1 shows the frequency of case submissions from full member countries of the WHO Programme during the first six months of 2006. Altogether 52 out of 81 member countries have submitted reports to the UMC during the first half of 2006. The minimum requirement of sending reports to the UMC is four times per year.



Graph 1



Graph 2

### Cumulative reporting

Graph 2 shows the cumulative reporting from the start of the WHO Programme in 1968 up to the 4th of September 2006.

\* a batch can consist of one up to tens of thousands of reports, depending on the reporting country.

# WHO Vaccine Safety Team visits the UMC

As a first step in the implementation of the recommendations made by the WHO Consultation on Global Monitoring of Adverse Events Following Immunization (AEFI) (see page 20 of this UR), a team representing WHO vaccine safety visited the UMC on 28 and 29 September, 2006. Members of the team were Adwoa Bentsi-Enchill and Dina Pfeiffer from Vaccine Quality Safety and Standards, Shanthi Pal from Quality and Safety of Medicines, and Stephen Evans (of the London School of Hygiene and Tropical Medicine), representing the Global Advisory Committee on Vaccine Safety.

Technical experts from UMC presented methods and processes used at the UMC for data management, database retrievals, signal identification and analysis, including data mining techniques. Discussions were held on how these tools could be adapted and used for the specific analysis of vaccine safety data. Of special concern was the finding of a recent investigation showing that very few countries submit a significant number of vaccine-related adverse reaction reports to the WHO database at the UMC. Ideas were shared on how to promote vaccine reporting and on how to extend the network of the WHO pharmacovigilance programme to include more vaccine monitoring centres. It was agreed that some of the tools used for coding vaccine products, i.e. the WHO Drug Dictionary and the ATC system, would need revision to fully meet the needs of the vaccine safety team. The WHO team offered to actively search for sources of funding to support the UMC in improving the vaccine part of the Drug Dictionary. It was also suggested that a professional appointed by the vaccine safety programme would be working with the UMC's signal analysis team, specifically focusing on the development of methods adapted for vaccine signal identification and analysis.



*Dina Pfeiffer and Adwoa Bentsi-Enchill from WHO Vaccine Quality Safety and Standards, and Shanthi Pal from WHO Quality and Safety of Medicines*

During the meeting a discussion was also held regarding the WHO planning for a possible outbreak of an avian flu pandemic and to what extent the UMC might be able to assist in monitoring the safety of vaccines used in that situation. No firm conclusions were reached. It was noted that on this and many other issues there need



*Andrew Bate and Stephen Evans in discussion*

to be closer contacts between the UMC and the WHO vaccine safety team in the future. It was felt from both sides that this meeting was long overdue.

## Vaccines monitoring – the way forward

At its June 2005 meeting, WHO's Global Advisory Committee on Vaccine Safety (GACVS), while acknowledging the work of *the UMC* in analysing drug-related adverse events, perceived limitations in the monitoring of vaccines safety, including the small number of reports made to *the UMC* and the limited information in those reports. The inherent difficulties in using signalling tools developed for non-vaccine-related adverse drug reactions and problems communicating vaccine safety signals of potential adverse reactions were also noted. The GACVS recommended that WHO convene international experts to discuss means for improving the reporting and analysis of information on vaccine safety globally. Participants at the September 2005 annual meeting of national centres supported this initiative and raised a number of issues to be deliberated.

The consultation, held in Geneva, on 9–10 January 2006 was jointly organized by WHO's Department of Medicines Policy and Standards and the Department of Immunization, Vaccines and Biologicals. Experts from WHO, representatives from selected national pharmacovigilance centres, drug regulation authorities, experts on immunization and vaccine safety, members of the Brighton Collaboration and representatives of the pharmaceutical industry and the GACVS assembled.

The objective of the meeting was to review the current status of monitoring of adverse events following immunization and make recommendations on building a high-quality global monitoring system.

As part of the consultation, participants were informed of ongoing activities. Currently, only 35% of 192 Member States, and only 25% of 165 non-industrialized countries, have an adequately functioning system for monitoring adverse events following immunization.

The recommendations were as follows:

### *Improving reporting to UMC of immunization-related adverse events*

- (i) Countries are encouraged to report adverse events following immunization through their government's designated national pharmacovigilance centre.
- (ii) If a national government finds it necessary to maintain separate reporting systems, then a monitoring centre for immunization-related events may be recognized as an additional reporting centre to *the UMC*.
- (iii) Where there is no national pharmacovigilance centre, a monitoring centre for immunization-related events should be designated to send reports to *the UMC*. In such situations, countries are encouraged to expand monitoring to cover all aspects of drug safety reporting.
- (iv) Further work is needed to explore the determinants of reporting immunization-related events.

### *Improving resources and methods for reporting and analysis*

- (i) Vigibase online, a web-based tool for reporting adverse drug reactions, should be made available to countries to help them improve reporting of immunization-related events in a timely and efficient manner.
- (ii) A focal point for vaccine-related reports should be identified at national pharmacovigilance centres (for national data) and at *the UMC* (for global data).
- (iii) Terminology used for vaccine-safety monitoring should be further developed and harmonized. The use of Brighton Collaboration case definitions should be encouraged, as should further guidance from the CIOMS Working Group.
- (iv) Poor quality reports should not be omitted from the database, because developments in signal analysis and other analytical methods may permit better evaluation in the future.
- (v) Signal search strategies will need to be developed specifically for vaccines (using the product, antigen, additive, adjuvant or other vaccine constituent).
- (vi) The signal review panel at *the UMC* should be strengthened to include more experts in vaccine safety.
- (vii) Joint training activities are to be encouraged for vaccines and other adverse drug reactions, and for regulators, particularly through UMC courses on pharmacovigilance and the Global Training Network course on adverse events following immunization.
- (viii) The ATC classification system should be able to differentiate between types of vaccines, such as conjugate, polysaccharide, acellular, whole cell, monovalent and multivalent. A working group should address these issues.

See <http://www.who.int/wer/2006/en/> for more details

### **Youth and Medicines report**

A report from the international conference held in Marholmen, Sweden on 1–3 June 2005 has been published, and is available from Kilen ([kilen@kilen.org](mailto:kilen@kilen.org) ; Tel +46 (0)8 696 0100). It has transcripts from the speakers, among others Ralph Edwards, Pat Bush and Barbara Mintzes, and country presentations from young people.

A revised Youth and Medicines Consensus Statement and a DVD of the conference are also available.

# Dangerous Doses

by Katherine Eban

Harvest Books Harcourt Inc. 2005

## Review by Kenneth and Catherine Hartigan-Go

A true story of counterfeit medicines and sub-quality drugs, this book recounts how a few pharmacovigilantes, good people who call themselves the 'Horsemen of the Apocalypse', banded together to stop criminals from hurting innocent patients with harmful drugs in the USA.

This gripping book is a must-read for all drug regulatory authorities worldwide, particularly the WHO national centres undertaking drug monitoring. We need to understand how the criminal mind works and the paradigms by which they operate. Only then can we develop a new breed of drug regulators, with better tools to detect drug product problems including bad practices, and the mechanisms to share these data with investigators.

Greed coupled with regulatory loopholes, such as a lack of checks and balances, paved the way for outlaws to dilute drugs, fake medicines, change labels and sell these ineffectual substances to legitimately licensed wholesalers, distributors and retailers. As long as legitimate drug industry players are willing to purchase cheaper substandard medicines, stolen, adulterated, diluted, or diverted from unscrupulous sources for a larger profit, such nefarious activities will prosper. The book describes how these medicines inflict patients, including children, with life-threatening conditions.

Bureaucrats still define 'drugs' as dependence-producing illicit substances of abuse and have not demonstrated a sense of urgency in addressing problems with legitimate drugs. When state inspectors report bad practices, senior civil servants ignore the writing on the wall, blind to the impact of their inaction. Worse is what the leakage of confidential investigative information may imply about them. Only at the end, when all the work is done, do they take credit for the work of the 'Horsemen of the Apocalypse'.

The book also affords a peek into the lives of these pharmacovigilantes, including the difficulties they endure for walking that extra kilometre in the search for truth. One advantage they have is their supportive partners who understand the nature of their work and who are victims of collateral damage and death threats at times. Society rarely acknowledges their contribution.

Conversely, the villains live a lifestyle of debauchery, extravagance, deceit, sexual misconduct and psychopathic behaviour. Nevertheless, their partners and mistresses are equally supportive of their misconduct. Villains can be disguised as the normal Joe-next-door types, or even leaders and stewards of community spirit.

Inaccessible medicines, whether due to price or availability issues, make it tempting for both traders and unsuspecting patients to take advantage of what they believe is a bargain deal. This book tells of legitimate drug companies setting up illegitimate businesses, and legitimate wholesalers undermining and circumventing the legislative system in order to delay or altogether avoid submitting pedigree papers.

Unethical business practices must be nipped in the bud; industry association lobby may be the norm in some countries, but it compromises the political infrastructure, effectively clipping the mandate of regulators, empowering criminals in the process. Akin to sleeping with the enemy, these unethical practices by industry contribute to pharmaceutical terrorism.

Of late, doctors and health care professionals have been reporting more therapeutic failures, type F adverse drug reactions (ADRs). *the UMC* stated that inefficacy of medicines ranks 7th among the reasons for adverse drug events in 2005 (personal communication, Ralph Edwards, 2006).

Some argue that the first order of business is to deliver life-saving public health drugs to people who urgently need them, relegating quality to a lower priority. However, providing a community access to ineffective, unsafe medicines may be worse than not giving them medicines at all.

The situation must be remedied, or else drug regulators may become unable to ensure quality of medicines, compromising public health. This book serves as a wake-up call to regulators, government officials, clinicians and patients, and the pharmaceutical industry. It also provides strong advocacy for pharmacovigilance to have the necessary investment it so deserves.

## Pharmaceutical Toxicology

Safety sciences of drugs (First edition)

Edited by Gerard J Mulder - Leiden Amsterdam Center for Drug Research and Lennart Dencker - Professor and Chairman of Toxicology; Dean, Faculty of Pharmacy at Uppsala University

This is the first title in the ULLA Series: a new and innovative line of introductory textbooks on pharmaceutical science for postgraduate students produced by the ULLA Consortium (European Consortium for Advanced Pharmaceutical Education and Research).

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4. Teratology
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6. Carcinogenicity of Drugs
7. Liver Toxicity
8. Kidney Toxicity
9. Toxicology in the Respiratory System
10. Immunotoxicity
11. Clinical Toxicology
12. Safety Assessment of Pharmaceuticals: Regulatory Aspects
13. Pharmacovigilance

£29.95

ISBN: 0 85369 593 8

Paperback, 272 pages

## VigiFlow

### a new name and less confusion?

*the* UMC provides a number of services to National Centres and commercial companies. We are now in the process of introducing our services to a wider audience and are therefore modifying some product names, to avoid confusion. The terms Vigibase Online and Vigibase have often caused confusion – which of them is the WHO-ADR database and which is the ADR management tool?

Vigibase is the WHO-ADR database and Vigibase Online is the ADR management tool through which National Centres can send reports to Vigibase, but most important – use for their ADR management. However, this is not entirely clear in the names.

To avoid further confusion, in future Vigibase Online will change its name to VigiFlow. The new name VigiFlow, represents the flow of ADR reports in the system and the flow of time, since time is an important aspect in pharmacovigilance work. It also clarifies that VigiFlow is a tool in itself and not just an interface for national pharmacovigilance centres to report to the WHO-ADR database (see p10-11 of UR32 for a description of the GxP validation process).



*UMC staff presenting VigiFlow at the ICPE conference in Lisbon, from left: Mats Persson, Magnus Wallberg, Annika Wallström, Kristina Johansson.*

Please note that there are no other changes in the software except for the new name. If you are a user you will have noticed the new name when the version of the software was released at the end of September.

The VigiFlow software can now be set up with a 'company profile'. The company profile is built for small pharmaceutical companies that need a cost-efficient, easy-to-use ADR management tool. Companies which subscribe to and use VigiFlow cannot send their reports to Vigibase through the system, but they can use the XML export function to send reports to regulatory authorities. VigiFlow was introduced to commercial customers at the ICPE Conference in Lisbon in August.

## Meet the team

Staff from UMC Products and Services are planning to be present at the following conferences:

29-30 January 2007

DIA CDM Japan + DIA SIAC, Tokyo, Japan

25-28 March 2007

DIA Euro Meeting + DIA SIAC, Vienna, Austria

18-20 March 2007

DIA CDM USA + DIA SIAC, Orlando, FL, USA

27-28 March 2007

ICC, Birmingham, UK

17-20 June 2007

DIA Annual Meeting USA+ DIA SIAC, Atlanta, GA, USA

## User Group

We are planning two User Group meetings during 2007, one in Europe and one in the USA. The exact dates and venues will be announced on the User Group portal on the UMC Products and Services website [www.unc-products.com](http://www.unc-products.com). The User Group Portal has much to offer both new customers and experienced users alike.

# COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
18-21 October 2006	The Role of Communication in Patient Safety and Pharmacotherapy Effectiveness	Vienna, Austria	European Society of Clinical Pharmacy Tel: +32-2-743 1542 Fax: +32-2-743 1550 E-mail: info@escpweb.org www.escpweb.org
1-2 November 2006	Introduction to Pharmacoepidemiology	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dru.org
2-3 November 2006	Safe Studies throughout the life cycle – a cradle to grave approach	Paris, France	DIA Fax : +1 215 442 6199 www.diahome.org
9-10 November 2006	Pharmacovigilance – A Blueprint for Risk Management – 12th Annual Training Course in Pharmacovigilance	Ottawa, Canada	KUSURI Canada Corp. PO Box 8304, Stn. 'T', Ottawa, Ontario, Canada Tel/fax : +1 (613) 523-5993
15-16 November 2006	Case Narrative Writing for Reporting Adverse Events	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dru.org
27 November – 1 December 2006	Excellence in Pharmacovigilance – Clinical Trials and Post Marketing	Paris, France	DIA Tel: +41 61 2255142 E-mail: janet.doyle@diaeurope.org
4-5 December 2006	1st Annual Cardiac Safety Conference	Berlin, Germany	DIA E-mail: tatjana.topalovic@diaeurope.org
24-26 January 2007	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@dru.org
10 February 2007	Pharmacovigilance – Introductory course	London, UK	Management Forum Ltd Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 www.management-forum.co.uk
11 February 2007	Pharmacovigilance: Compliance and Quality Assurance	London, UK	Management Forum Ltd Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 www.management-forum.co.uk
13 February – 13 July 2007	Certificate in Pharmacoepidemiology & Pharmacovigilance (20-week course)	London, UK	London School of Hygiene and Tropical Medicine Tel: +44 (0)20 7299 4646 Fax: +44 (0)20 7323 0638 E-mail: registry@lshtm.ac.uk www.lshtm.ac.uk/
22-23 March 2007	Safety of immunotherapy development and patient care	Budapest, Hungary	International Society of Pharmacovigilance Tel/Fax: +44 (0)20 8286 1888 www.isoponline.org
11-13 April 2007	28ème journées de pharmacovigilance	Toulouse, France	Secrétariat de la Société Française de Pharmacologie et de Thérapeutique Tel: +33 2 35 14 86 04 Fax : +33 2 35 14 86 09 E-mail : secretariat@pharmacol-fr.org
21-23 April 2007	ISPE Mid-Year Meeting	Amsterdam, Netherlands	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
14-26 May 2007	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
15-17 June 2007	Basic Course in Pharmacovigilance	London, UK	Management Forum Ltd Tel: +44 (0)1483 570099 Fax: +44 (0)1483 536424 Website: www.management-forum.co.uk



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