WHO-UMC 33

UPPSALA REPORTS April 2006

For everyone concerned with the issues of pharmacovigilance

10 years of Uppsala Reports

Focus on Africa

Medication Error

Nurse reporting

Drug Safety and the EU

10th anniversary edition

DIRECTOR'S MESSAGE

Ralph Edwards
Director
the Uppsala Monitoring Centre

Uppsala has had heavy snowfall over 4 days in early March this year. Beautiful, disruptive also, but life has not been greatly affected. There have been more minor accidents, and some delays to public transport, nothing more.

This is a big contrast with when I lived in the UK and in New Zealand where small amounts of snow caused more accidents, more delays and was generally very much more troublesome. It is easy to think why this is so even now:

- Lack of preparedness: not enough snow clearance or road salting, no winter tyres or chains, wrong clothes
- Risk aversion: the public don't know how to handle activities under snowy conditions; many don't go to work and schools are closed
- Risk taking: inexperienced drivers drive too fast and with the wrong techniques.

The paradox that both risk taking and risk aversive behaviour occurs at the same time divides people into groups. Both result from limited knowledge, but it seems to me that the risk averse have not only different personalities, but also have been scarred by their negative experiences which they have failed to balance with the positive. Risk takers are more likely to be inexperienced in negative outcomes!

It is also easy to apply this commonplace example of risks to drug risks:

- Lack of preparedness. Most of the public and many health professionals do not even think of the possibility of drug risks. When they do, it is in a panic state both personally and in the public media. More negative incidents are inevitable when there is snow, as when taking drugs, but that should not stop cautious driving: one simply needs to know what to do, to minimise the risks, not panic over them. Having the right education and equipment is essential for this. (The 'right equipment' will become more true for some difficult medicines at least, such as the improvements in safety made possible by self-monitoring)[1,2]
- Risk aversion: follows from lack of preparedness. Far too many patients are afraid of taking medicines because they have a false perception of the risks and are ill-prepared to deal with them. I wonder how many patients are more harmed by not taking medicines properly, than by taking them? If anyone has up-to-date figures on this please tell me
- Risk taking is usually the health professional's dubious role. They, particularly the inexperienced, do not treat drugs, particularly new ones, with enough respect. Constant monitoring of the outcomes of therapy in patients is always desirable, but the more so when experience with the drug is limited.

A final thought. Snow melts and its risks are gone. I wish we could do the same with the risks of medical therapy!

1 Richardson E. Self-monitoring of oral anticoagulation. Lancet. 2006 Feb 4;367(9508):412.
2 Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perera R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and meta-analysis. Lancet. 2006 Feb 4;367(9508):404-11.

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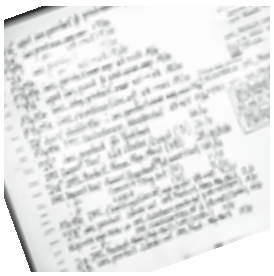
Another milestone in the development of the world's most comprehensive dictionary of medicinal product information.



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Drug Safety Monitoring in Belarus

Svetlana Setkina writes

Republican Clinical-Pharmacological Laboratory of Centre for Examinations and Testing in Health Service: Dr Voronov G Gennady, MD, PhD, Chief of the Laboratory, Ph Setkina B Svetlana, senior specialist

"Some remedies are worse than the disease" Publilius Syrus, Roman writer, 1st century BC. Living in the 21st century we would add to this ancient saying understanding of drug safety problem: "in some circumstances some remedies are worse than the disease".

The Republic of Belarus was accepted as the 79th participant in the WHO Programme for International Drug Monitoring on 19th January 2006. We much appreciate this decision since membership not only provides us with unique possibilities in the sphere of pharmacovigilance communication, research and information, but also means for us a new level of activity through incorporation in the international pharmacovigilance team.

Our country

Republic of Belarus is an independent country located in eastern Europe, with a population of about 10 million people. The government policy is socially oriented and people are provided with free medical and health care.

History of Pharmacovigilance Programme

In 1997 the Centre for Examinations and Testing in Health Service was established, which undertook among its tasks the medicines authorization function and maintenance of the drug registry. The Centre for Examinations and Testing in Health Service was appointed by the Ministry of Health to become the structure responsible for organization of ADR monitoring and simultaneously mandatory ADR reporting by health professionals was implemented. In 2003 detailed instructions for healthcare professionals were developed which implemented internationally accepted terminology, a national ADR reporting form, and specified the healthcare specialists to be involved in this system. The national pharmacovigilance programme gained its strength within 2004 and 2005 leading to full membership of the WHO Drug Monitoring Programme.

Strengths and weaknesses

Our strong point is that organizing pharmacovigilance activity on the basis of the Centre for Examinations and Testing allow us to implement appropriate regulatory measures, to carry out effectively decision-making procedures and related actions. Although regulatory action is considered an intermediate goal of pharmacovigilance, correct operation with this tool is helpful on the initial steps of activity.

Our weak point, as in many other countries, is the tradition of ADR monitoring activity among healthcare providers is only just beginning, which significantly delays the establishing of an effective domestic ADR reporting network. Our aim is to provide safe, effective and rational use of marketed drugs.

Functions and activities

At present the following functions are carried out by our Unit:

- running the domestic ADR database with quick feedback to the reporting healthcare professional by a personal letter;
- submitting suspected ADR information to *the* UMC by Vigibase Online;
- collecting and analyzing available current safety information with subsequent appropriate actions (regular safety alerts informative letters and publications for healthcare professionals, safety related SPC changes and all procedure benefit-harm-risk profile updating until voluntary or obligatory withdrawal);
- promoting local ADR reporting; creating an awareness among healthcare providers about the importance of ADR monitoring activity (informative materials, regular lectures on pharmacovigilance and drug safety within the SCP training course for post-graduate specialists);
- detailed evaluation of the data generated through pharmacovigilance activity, causality assessment, decision-making process;
- international cooperation in the pharmacovigilance sphere;
- contributing to the drug authorization and renewal procedure;
- contributing to the drug advertisement control procedure.

Building on the foundations

Drug safety monitoring is a public-health activity and we are aware of our responsibility for creating an effective pharmacovigilance system. Besides increasing the number of our functions, as the National Pharmacovigilance Unit, our efforts are directed to working with other parties - healthcare providers, researchers, the pharmaceutical industry, academia and others - for further development and optimization of national pharmacovigilance, making it an integral part of health care system to ensure patient safety.

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Madagascar – island with a bright (PV) future

Alex Dodoo reports

Antananarivo, the capital of Madagascar, provided the perfect panoramic backdrop for a 2-day planning workshop from 2nd to 3rd February on the establishment of pharmacovigilance in Madagascar.

From left to right: Alex Dodoo, Rachida Soulaymani, Dr Jean René Randriasamimanana, Esperanca de Sevene, Dr Donat Rakotomanana, at the meeting in Antananarivo.

The workshop, jointly organised by the Malaria Action Coalition (USAID, CDC, MSH) was attended by over 50 participants. The Minister of Health, Madagascar, the WHO Country Representative and the USAID Country Director were all represented at the opening ceremony. A combination of lectures and small group discussions was used to explain the importance of pharmacovigilance and how the WHO Programme for International Drug Monitoring operates. Country experiences were shared by the heads of pharmacovigilance of Morocco (Rachida Soulaymani), Mozambique (Esperanca de Sevene) and Ghana (Alex Dodoo). The rich and varied experiences of these three countries was well appreciated by participants and firm plans have now been made for a formal 2-week 'training of trainers' international pharmacovigilance workshop in April or May 2006. The Madagascar ADR forms ('fiche de notification') which were developed at the workshop are currently being field-tested in four health facilities in Antananarivo.

The most well-known picture of Madagascar - Antananarivo the capital - with its hills and valleys.

The Director of the Agence du Medicaments de Madagascar (DAMM) Dr Jean René Randriasamimanana whose strong support and enthusiasm for the project has led to the rapid progress seen this year was full of praise to WHO and the Malaria Action Coalition partners for the technical assistance received. Dr Donat Rakotomanana, head of the pharmacovigilance department of DAMM will coordinate and liaise with the WHO.

West African focus on Pharmacovigilance

The West Africa Network for Monitoring Anti-malarial Treatment (WANMATT) is a sub-regional grouping of six Francophone (Benin, Burkina Faso, Cote d'Ivoire, Mali, Niger, Togo) and three Anglophone (Ghana, Nigeria, Sierra Leone) countries whose vision is to share experiences and good practices in monitoring the efficacy of anti-malarial treatment.

The group already has a database on anti-malarial drug efficacy and resistance. The potential WANMATT offers for incorporating pharmacovigilance into public health programmes is so huge that the Ghana Centre for Pharmacovigilance did not hesitate when it was requested by Dr Andrea Bosman (Roll Back Malaria, WHO Geneva) to facilitate a one-day workshop on pharmacovigilance for WANMATT. The workshop itself took place during the WANMATT General Assembly at Cotonou, Benin on 21st February 2006 and was facilitated by Alex Dodoo and Augustina Appiah-Danquah of the Ghana Centre. The 26 participants from all these countries found pharmacovigilance so interesting and extremely important that they issued a formal resolution to hold a longer workshop on pharmacovigilance as part of the WANMATT current plan of work.

The Director-General of WANMATT Professor Robert Tinga Guiguemde of Burkina Faso and the Policy Advisor Dr Walter Kazadi joined participants in expressing appreciation to the WHO for its work on pharmacovigilance and stressed the importance of collecting and sharing safety information within the network. *the* UMC and WHO-HQ supplied English and French versions of various materials on pharmacovigilance.

Associate Member Timeline

Sten Olsson

8th February
We receive a new application from a country wishing to join the WHO Programme, this time Botswana. Contact:
Motshegwana Olenkie Tebogo
Drugs Regulatory Unit
Ministry Of Health
Private Bag 0038
Gaborone
Botswana
Tel: (+267) 3180883/1/863/4/870/4/5 (W) (+267) 3959973
Fax: (+267) 3180870

Olenkie, an enthusiastic lady, attended *the* UMC pharmacovigilance course in May 2005.

22nd February
We receive an application from another African country wanting to join the WHO Programme – this week Madagascar. This is a direct effect of Alex Dodoo visiting a few weeks ago. Contacts between *the* UMC and l'Agence du Medicament du Madagascar were established 6 months previously when Mohamed Farah met one of their representatives at a meeting in South Africa. Contact person at the pharmacovigilance centre is Dr Donat Paul Etienne Rakotomanana.

10th March
Algeria has had a 'Centre National de Pharmacovigilance et de Materiovigilance' for some time but it has not had any relationship with *the* UMC. In June 2005 Ralph Edwards met the director, Professor Abdelkader Helali at a meeting in Geneva. Contact established, Dr Helali and I have exchanged messages and documents. Algeria becomes the 19th associate member of the Programme.

NEWS FROM AROUND THE WORLD

Costa Rica: training in Spain

Mariano Madurga writes

The National Centre for Costa Rica has been transferred from the 'Caja Costarricense del Seguro Social' to the Ministry of Public Health[1]. The Co-ordinator is Dr Adolfo Ortiz Barboza assisted by Dra Xiomara Vega. During three months (since 11th April to 3rd July 2005) both of them attended a training programme at the Division of Pharmacoepidemiology and Pharmacovigilance of the Spanish Medicines and Healthcare Products Agency (AGEMED). This training programme was co-ordinated by Mariano Madurga.

Dra Xiomara Vega and Dr Adolfo Ortiz (right).

During this time, they received induction in several concepts and strategies of pharmacovigilance: assessment and managing of adverse drug reactions, national pharmacovigilance programmes, spontaneous reporting systems, post-authorisation safety studies, the WHO International Drug Monitoring Programme with sessions about Vigibase Online, etc. Furthermore, they were trained about the daily work of the Pharmacovigilance Regional Centre of Madrid during 20 days: yellow cards, acknowledgments to reporters, bulletins, website publications, ADR evaluation and entering data into FEDRA (database), signal detection, etc. They also attended a meeting of the 'Comité Técnico de Farmacovigilancia' technical committee with 17 Regional Centres of the Spanish System, and a meeting of the 'Comité de Seguridad de Medicamentos de Uso Humano', the Committee on Safety of Medicines of AGEMED.

We hope that this training gives them enough expertise in pharmacovigilance to set up the new National Centre in Costa Rica, to build on the previous experience from the pharmacovigilance centre of 'Caja Costarricense del Seguro Social', through the good works of Dr Albin Chaves.

1. Change in Costa Rica. Uppsala Reports, October 2005: nº 31: 6

MedWatch – FDA Safety Information and Adverse Event Reporting Program

An alert to a new FDA service, from Sten Olsson

FDA Patient Safety News (PSN) is a monthly video news show for health care professionals. It covers significant new product approvals, recalls and safety alerts, and offers important tips on protecting patients. Anyone with a reasonably fast download on their computer can read the complete stories and watch or download the video at: http://www.fda.gov/psn.

Readers on the MedWatch circulation list may have already received notification of some of these safety issues. However, many PSN stories contain video footage and demonstrations that may be useful to educators in healthcare facilities and academic institutions. Although obviously aimed at an audience in the USA, the videos will have much interest to health professionals in other parts of the world.

As an example, the March 2006 edition included a 1½ minute clip about Tamiflu ('Tamiflu Approved for Flu Prevention in Children Under 12'):
http://www.accessdata.fda.gov/psn/transcript.cfm?show=49#1

Netherlands

Kees van Grootheest, Director of the Netherlands Pharmacovigilance Centre, Lareb describes an important feature of their website

The Lareb website is frequently visited by other pharmacovigilance centres in the world. It gets visitors from all over the world and some centres use information to confirm their own signals or to find background information.

Since February last year, the search function on our website <http://www.lareb.nl/bijwerkingen/zoeken.asp> gives access to the Netherlands national adverse drug reaction database. This function has recently been improved and the information in the database and website is easier to access.

You can view all reports on a specific drug, or you can expand your search results to similar drugs. Choose 'English' in the right upper corner to get the results in English. At the end of the search results you will find links to relevant Lareb publications, both in English and Dutch.

To try it out, go to:
http://www.lareb.nl/bijwerkingen/zoekresultaten.asp

Drug Monitoring in Croatia

A report on recent changes from Viola Macolić Šarinić

Croatia is a beautiful European country with both continental and Mediterranean attributes. We are well known for our lovely coast with numerous islands which is a resort for thousands of tourists during the summer.

National Programme history

The importance of adverse drug reactions monitoring was recognised in Croatia already in 1974 when the National Centre for adverse drug reactions monitoring was instituted in Zagreb, Croatia's capital. At that time, Croatia was a part of former Yugoslavia and the National Centre in Zagreb received all ADR reports from the regional centres. In 1978 National centre for adverse drug reactions monitoring joined the WHO Programme for International Drug Monitoring.

In 1991, when Croatia became an independent country, the former Yugoslav National Centre in Zagreb continued its work as Croatian National Centre, which represented our country as a full member of the WHO Programme from 1992.

Introducing the Agency

In March 2005, after new legislation came into force, the obligation of both pre- and post-marketing drug safety surveillance was delegated to the Agency for Medicinal Products and Medical Devices (instituted in October 2003). The Agency's Pharmacovigilance unit with its two sub-units was than formed: a sub-unit for adverse reactions arising from clinical trials and a sub-unit for post-marketing adverse reactions.

Agency for Medicinal Products and Medical Devices, Zagreb, Croatia

Spontaneous reporting

Reporting requirements in Croatia are in accordance with current EU legislation and international guidelines and reporting of adverse reactions is mandatory for the health care professionals.

Spontaneous reports are sent to the Agency on our reporting form via post, fax, e-mail or in person. Every report is evaluated by the clinical pharmacologist and a written answer is sent to the reporter explaining possible mechanism of reaction, expectedness, causality and a recommendation on further action to be taken.

In 2005 the Pharmacovigilance Unit received 307 spontaneous reports from health care professionals for drugs and 159 for vaccines.

Activities

Since its formation, the Pharmacovigilance unit of the Agency has constantly encouraged physicians and other healthcare professionals to report suspected adverse reactions.

We have started a ***Workshop about the role of physicians and pharmacists in adverse reaction reporting and pharmacovigilance system in Croatia***. The workshops are free of charge and are recognised as a part of continuing education by the Croatian health care professionals chambers. We have organised 15 workshops in 4 different cities (Zagreb, Osijek, Rijeka, Bjelovar) with over 400 participants. During these workshops we became aware of the limited knowledge about adverse reaction reporting in our county and for that reason healthcare professionals found the workshop very useful for their everyday work. The results of our efforts will be seen in 2006.

Head of Croatian Agency Sinisa Tomic and employees during a recent visit to the UMC.

Our web-site (www.almp.hr) is regularly updated with pharmacovigilance news and regulatory actions taken in connection with safety of medicines. Staff of our unit have also made their contribution in under- and post-graduate education as guest-speakers (Medical school, Zagreb and Rijeka, Zagreb Health School). We also organised a Workshop for Qualified Persons in Pharmacovigilance in November 2005, and our next project is a Seminar about Periodical Safety Update Reports that is to be held in April 2006.

Following our findings that there are many uncertainties and misunderstandings with reporting of adverse events/reactions arising from clinical trials, we are also planning to organise several workshops for the investigators, sponsors and contract research organisations by the end of this year.

Head of the Agency: Assistant Professor Šinisa Tomić PhD

Contact Person for Pharmacovigilance:
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Footnote Professor Igor Francetic and his team will remain part of the WHO Programme network.

The collaboration of the EU pharmacovigilance system with WHO

Priya Bahri, PhD

European countries have a long tradition of working with the World Health Organization (WHO) in the field of pharmacovigilance. The WHO Programme for International Drug Monitoring was brought to life in 1968, and half the founding members now belong to the European Union (EU)[1]. By 2006 all 25 EU Member States have joined the WHO Programme (apart from one which is in the process of joining).

EU pharmacovigilance system – its creation

EU Member States co-operate with each other in a European framework, which by now has become the so-called EU pharmacovigilance system. Following many years of informal co-operation, the base for a formal system was provided in 1993 through introduction of the pharmacovigilance concept into Council Directive 75/319/EEC[2], the Pharmaceutical Directive. Thereby, the national pharmacovigilance systems were given a common legal basis and reference for standard setting.

The European Agency for the Evaluation of Medicinal Products, now the European Medicines Agency (EMEA), became operational in 1995 (Council Regulation (EEC) No. 2309/93[3]) and provides co-ordination of the system. This has a networking structure with defined responsibilities for all regulatory partners, i.e. Member States, the European Commission and the EMEA, and uses a common database for adverse reaction reports (EudraVigilance).

Legal provision for collaboration with WHO

The Council Regulation also included a specific article requiring the EMEA to collaborate with WHO on pharmacovigilance matters and to submit information on measures taken for medicines in the EU which may have a bearing on public health protection in other countries. This is now included in the revised legislation as Article 27 of Regulation (EEC) No. 726/2004[4].

In order to implement this legal provision and to enhance the collaboration, a guideline was issued by the EMEA in 1998 and later included in Volume 9 of the Rules Governing Medicinal Products in the EU[5]. Volume 9 is currently subject to an in-depth review[6], including a review of guidance on the collaboration with WHO. The revised draft was presented, prior to its release for public consultation, at the 28th Annual Meeting of the WHO Programme in 2005 and very much welcomed by the participants, as it provides for strengthened collaboration in the future.

EU pharmacovigilance system – responsibilities

The principles of the collaboration between the EU and WHO correspond to the allocation of pharmacovigilance responsibilities to the various regulatory partners for the three different types of marketing authorisations in the EU:

(a) Centralised marketing authorisations are issued by the European Commission and are valid in all Member States. Pharmacovigilance for these products is conducted by the EMEA with its committees and working parties.

(b) Marketing authorisations processed through the mutual recognition and decentralised procedures are issued by the competent authority in each Member State where the pharmaceutical company applies. The Member State where the product is authorised first, i.e. the Reference Member State, takes the lead for pharmacovigilance and harmonised action on behalf of all other Member States, while each national competent authority remains responsible for the authorisation.

(c) For purely nationally authorised products the competent authorities in the Member States are responsible for pharmacovigilance but may use informal mechanisms for harmonisation across the EU.

Collaboration with WHO

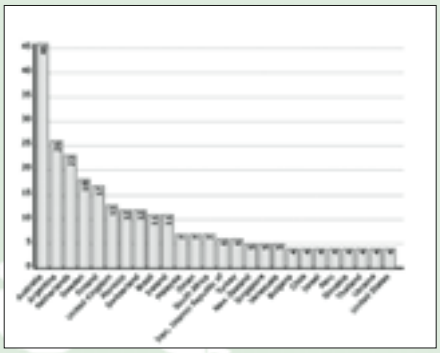
The guidance[6] on Article 27[4] details the following principles:

- Individual case safety reports are provided to the WHO Collaborating Centre (*the* UMC), for inclusion in the WHO database, by the competent authority of the Member State where the reported reaction occurred, in line with their obligations as members of the WHO Programme.
- National competent authorities as well as the EMEA consider the signals raised by *the* UMC in the document 'Signal'.
- For centrally authorised products, the EMEA provides WHO and *the* UMC with public statements on safety-related regulatory action prior to embargo date and replies to queries transmitted via Vigimed, the information exchange system for the WHO Programme. For products authorised through the mutual recognition and decentralised procedures, the Reference Member State will provide such information, and for purely nationally authorised products the Member States individually.
- Representatives from the Member States and the EMEA are encouraged to participate in the Annual Meetings of the WHO Programme.

Products used outside the EU

On the basis of Article 58 of Regulation (EEC) No. 726/2004[4], the EMEA may, in co-operation with WHO, give scientific opinions also for products intended exclusively for markets outside the EU. The holder of such opinion, usually a pharmaceutical company, should submit reports of adverse reactions to the competent authorities of the countries where the product is marketed as well as to EudraVigilance. Furthermore, it has to submit periodic safety update reports to the EMEA who may conduct a benefit-risk review at any time as necessary. Additional pharmacovigilance obligations and risk minimisation measures may be recommended in collaboration with the concerned country[7].

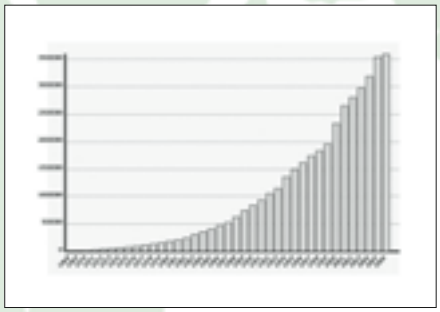
Reporting to the WHO database



Graph A

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 in Uppsala (also known as 'Vigibase'). The figures are correct for the end of March 2006.

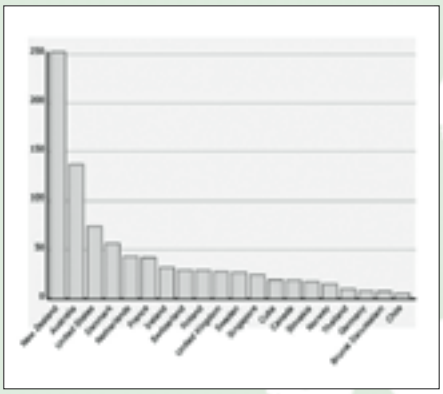
Graph A shows the frequency of case submissions from our member countries during 2005. Only 26 out of 78 countries (Brunei Darussalam, Lithuania and Mozambique new full members during 2005) fulfilled the requirement of sending reports to *the* UMC, where four times per year is the minimum requirement.



Graph B

Argentina, Brazil, Morocco, Switzerland, and Turkey are all active Vigibase Online users.

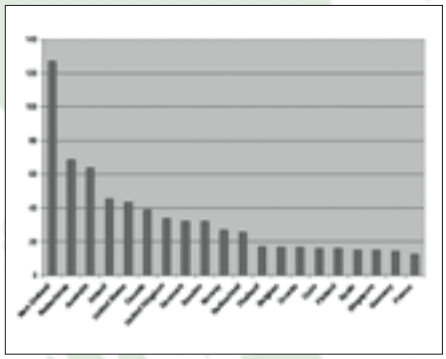
Graph B shows the cumulative reporting from the start of the WHO Programme in 1968 to 20060322. We have now more than 3.6 million correct and active case reports (3,600,802 reports to be exact) in Vigibase.



Graph C

Graph C shows the top 20 countries in terms of number of correct and active cases/100,000 inhabitants submitted during 2005.

The average for all countries is 14.3



Graph D

Graph D shows the top 20 countries in terms of number of correct and active cases/100,000 inhabitants during 2001-2005. The majority of the top countries have been members since the start of the WHO Programme.

The average for all countries is 10.5

continued from page 8

Outlook

The principles for pharmacovigilance collaboration of the EU with WHO have been followed since 1998, but there should be focus on adhering to the now expanded principles by all EU partners. Moreover, Article 58 will result in increased collaboration with WHO and countries outside the EU on product-related pharmacovigilance and risk management. Further collaboration will be considered as need arises. The EU is committed to provide their contribution to international health by promoting the safe use of medicines and supporting the worldwide development of pharmacovigilance.

Acknowledgements

I thank my Head of Sector Dr. Panos Tsintis for his review of the manuscript. The views expressed in this article are those of the author and not necessarily those of the EMEA.

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Liège

Planning continues for the 2006 Annual Meeting of the WHO Programme for International Drug Monitoring. The meeting will take place at the Palais des Congrès in Liège, Belgium from 9-11 October 2006, with a welcome reception at 19.00 on Sunday 8th October.

The questionnaire to prompt suggestions for the programme was posted on *the* UMC website in mid February with four weeks to return ideas to *the* UMC. Suggestions for topics to be covered in Liège were received and incorporated in the programme planning. The draft programme will be sent to member countries in May 2006.

The joint afternoon session with the International Society of Pharmacovigilance on Wednesday 11 October, entitled 'Prediction of risk in human drug use' will include talks on

- Genetic prediction of adverse drug reactions
- The implications of pharmacovigilance planning for developing countries: how this relates to the Public Health Programmes of WHO
- Risk perception in developing countries: the example of chlorproguanil/dapsone and amodiquine/artesunate
- Pharmacovigilance in the future: predictive pharmacology
- Joining forces for managing risks.

The ISoP conference details can be found at the website http://www.isop2006.org/

Official invitations to the WHO meeting were sent out to heads of pharmacovigilance in members countries from the office of Dr Mary Couper in Geneva at the end of March. Please do contact her if you think yours has not arrived.

On the social side...

The Official dinner is planned for 10th October in the 'Palais des Prince Evêques', preceded by a guided tour of the 'Episcopal Palace'. The ISoP welcome reception on the 11th will take place at the Museum of Modern Art in Liège, whose collection includes works by Monet, Pissarro, Guillaumin, Vlaminck, Magritte, Gauguin, Picasso, Chagall, Ensor and others...

Palais des Congrès alongside the Meuse river, Liège, Belgium

Big Response to Questionnaire

Sten Olsson wishes to thank all National Centre staff who have returned the detailed questionnaire about *the* UMC and the impact of its services and communications with external agencies. There has been an extremely high response rate, and National Centres can be assured that once the answers have been collated we will be dealing with all the points raised, both by individual countries and the more general issues which have arisen from this exercise.

It is not too late to return the form – we would still be pleased to have feedback from the countries that have yet to return the questionnaire.

Nurses as adverse reaction reporters

by Martin Bäckström

Improving reporting

Since spontaneous reporting of Adverse Drug Reactions (ADRs) was introduced in Sweden in 1965, it has been co-ordinated by the Medical Products Agency (MPA). To improve the general knowledge of several aspects of drug-related problems and reporting of ADRs, and to be able to form a national network for case–control studies, the first regional centre for spontaneous reporting was established in 1992 as a collaboration between the MPA in Uppsala and the Division of Clinical Pharmacology at the University Hospital in Umeå. The aims of regionalization were to increase the interest in drugs and drug-related problems within the health care system, to increase the number of reports, which would in turn enhance the possibility of detecting new and serious ADRs, to increase the amount of information in each individual report, and also increase the amount of information about drug-related problems to the health care system. The staff at regional centres consist of specially trained nurses, and at one centre also a pharmacist, who work in close collaboration with clinical pharmacologists in assessing and evaluating the reported cases, including giving prompt feedback to the reporters.

Under-reporting

In Sweden for several decades, it has been compulsory for health care professionals, licensed to prescribe drugs, to report suspected ADRs. However, we know there is a high degree of under-reporting, even of serious ADRs, in countries were the reporting rate has been considered to be high, for example France and Sweden [1, 2]. In Sweden doctors have been considered the best source for obtaining information about unwanted drug effects and ADRs. In other countries other methods in the spontaneous reporting system have been used for collecting ADR information: hospital pharmacists, consumer reports and nurses. In some countries these systems have been operating parallel with reports from physicians, and separate projects from these have also been developed. Several studies have shown that nurses report an equal proportion of serious ADRs compared with reports from physicians and GPs [3-5].

It is also well established that nurses can be a valuable source for obtaining information about suspected ADRs. Often they have close contact with patients, and in many cases they are in an ideal position for observing ADRs. In one study, performed at two departments of geriatrics in northern Sweden, during a 12-month period nurses received education about how and why to report suspected ADRs. The total reporting rate increased tenfold over the previous year [6]. Similar results have been shown in another study at four departments of internal medicine, infectious diseases and orthopaedics in three counties in Sweden [7].

Shared responsibility

Spontaneous reporting of suspected ADRs should be the responsibility not only of doctors and GPs, but also of health care professionals working in close contact with patients. Health care in Sweden and elsewhere is still a hierarchic system, where doctors, for historical reasons and due to their superior medical and scientific knowledge, are considered to be those who possess the skills to make necessary and important decisions, including reporting of ADRs. Reporting of suspected ADRs on a weak or often very weak suspicion is a very different approach to other duties and quite different from the way in which doctors are trained to deal with problems in patient care. It is possible that nurses in general could be more prepared to report ADRs only on suspicion.

Future directions

The national drug authority in Sweden (the MPA), has now proposed accepting reports from all nurses in the health care system. Reports from nurses will be handled according to existing routines, and the ADR reports will be stored in the national database for spontaneous reporting. Presumably this new group of reporters will improve the function of the reporting system in Sweden. This will require a small revision of the existing regulations, a matter that hopefully will be taken care of some time during the spring of 2006.

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UPPSALA REPORTS CELEBRATE

It is ten years exactly since the first edition of 'Uppsala Reports' rolled off the press and was despatched around the world. Much has changed in drug safety, in the UMC and in Uppsala Reports over the last decade so we thought it opportune to review the first 32 editions of our newsletter.

The first edition of Uppsala Reports came out in April 1996 and explained why *the* UMC was launching what was then a small newsletter:

- "To explain the Centre's work regularly and clearly to member countries and our wider audience
- To report and examine significant current issues in drug safety
- To share useful developments and discoveries from around the world
- To keep up-to-date with more personal and informal news."

A request in the first issue is also well worth repeating today:

- Please let us know if there are issues or questions you'd like us to deal with
- Send us information about developments and achievements in your department
- Tell us if you feel that Uppsala Reports is worthwhile for you
- Send us letters or articles for publication.

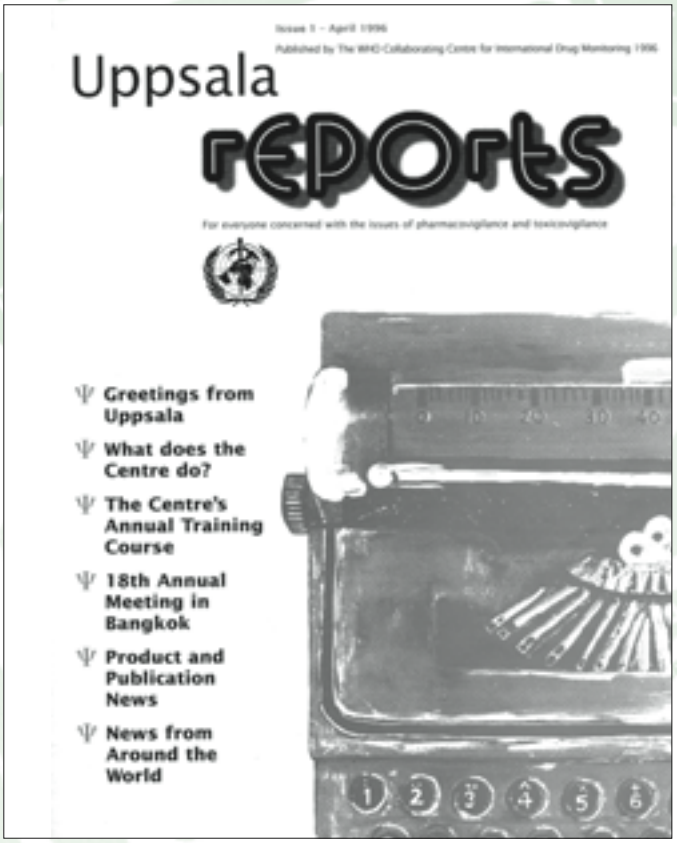
Uppsala Report No. 1 (consisting of six sides of A4) set out the mission and objectives of the Centre and listed its activities. As well as a group photo of the eleven staff, the issue included news on the latest version of the 'Critical Terms' list, a preview of the 4th UMC pharmacovigilance training course, a report from the 18th meeting of the WHO Programme meeting in Bangkok (53 participants from 31 countries attended), Product and Publication news and News from Around the World.

The early editions of Uppsala Reports closely reflect the concerns of the centre and the Programme. The 2nd issue contained a full-page explanation of the then signal detection method while the 3rd issue described the Centre's collaboration with Pharmasoft, a Swedish IT company (no longer in existence) which worked on the enhancement of IT capacity at *the* UMC and on the WHO database.

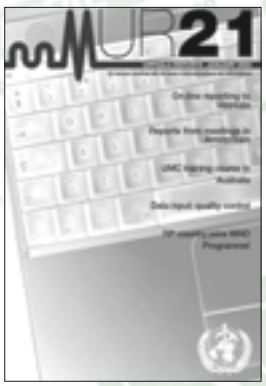
Uppsala Reports 5 in 1997 covered the move of the Centre to new premises at Stora Torget ('Big Square') in the centre of Uppsala. For issue 6 the newsletter expanded to 8 pages and celebrated the 30th anniversary of the WHO Programme. A copy of the Erice Declaration on good communication practice in pharmacovigilance was included with this edition. By issue 7 there were 53 members of the WHO Programme; reports from Ron Meyboom in Sudan and Mabel Valsecia and her regional pharmacovigilance centre in north-east Argentina complemented other news updates.

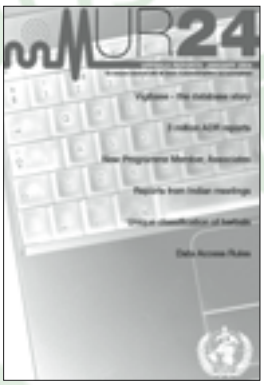
Uppsala Reports 8 coincided with an anniversary symposium, December 1988 in Stockholm, and enabled Ralph Edwards to take stock of where pharmacovigilance needed to go in future. The issue also recorded the sad death of Dr Susan Wood, head of the national centre in the UK, at the age of 46, and reported from the WHO Programme's Annual Meeting in Tokyo. The following issue had an interview with Martijn ten Ham, who had retired as head of the Drug Safety Unit at WHO.

With **Uppsala Reports 12** the publication increased in size to 12 pages and with many people from around the world visiting us in Uppsala



S TEN YEARS OF PUBLICATION





included the 'UMC's visitors' book', as well as introducing the ADRespherics data-mining service for commercial customers– sadly no longer on offer.

An interview with Dr Lembit Rägo, new head of the Quality Assurance and Safety of Medicines team at WHO headquarters, was published in **UR13**. In **UR14** the first of several occasional longer articles on more in-depths subjects was included; by Dr Kenneth Hartigan-Go of the Philippines, 'Pharmacovigilance and the Pursuit of Rational Drug Use' was presented as a loose insert. Other longer inserts have included one on monitoring herbal products and another 'Artemisia and Artemisinin, a story about toxicity'.

In **UR15**, the growing staff at Uppsala meant that an insert entitled 'UMC Basics' was included, listing all staff members with photos, their area of work and responsibilities and languages spoken. A questionnaire was also included asking for reader feedback.

UR19 was the first 20-page issue, and began a trend to longer, more detailed articles, while retaining the news snippets in 'News from Around the World' and 'News from Stora Torget'. Features on Drug Advertising to Consumers and Behind the Scenes at Reactions Weekly, along with an interview with Roland Orre about data-mining at *the* UMC offered substantial articles to readers.

UR21 in January 2003 had a big re-design, to tidy-up what had evolved from the first 6-page newsletter and become a substantial quarterly brochure. The first of our occasional series of 'profiles' featured Professor David Finney. It was followed later by profiles of Jan Venulet, Ed Napke and Bill Inman, all pioneers in pharmacovigilance.

UR24 (24 pages) had lively reports from around the world with in-depth explanation of the many complex work things we do – a prelude to the publication of Viewpoint 2 in early 2005.

The editor since the first edition has been Sten Olsson, who started work at the Centre in 1978. He, and co-editor Geoffrey Bowring, make the initial list of potential items, short and long, and where necessary commission the pieces from UMC staff or outside colleagues. He also regularly receives ideas and indeed ready-made features and accompanying photos to include in forthcoming editions. "We always try to ensure a broad international coverage with wherever possible news from all continents and from both experienced members of the Programme and newer members of the international drug safety community."

For the first five years Uppsala Reports was designed by a consultancy in London, printed in Birmingham in England and shipped out to Sweden. Currently, the designer is based on a remote farm in the north of England, but the printers are in Uppsala. The distribution list now contains more than 2,600 recipients in all continents of the world.

Sten Olsson, editor of Uppsala Reports

As well as having changed physically, the aims of Uppsala Reports have also evolved subtly from making the drug safety world aware of the existence of the WHO Collaborating Centre to covering activities of other groups and offering perspectives not otherwise available, including some historical accounts on the work of the WHO Programme and pharmacovigilance in general. Stories of the work of major, well established, pharmaco-vigilance centres might be under-represented in Uppsala Reports. This is an attempt to compensate a little for the fact that these centres often dominate in other media. Uppsala Reports wishes to reflect the development and expansion of pharmacovigilance not only methodologically but also geographically. Sometimes readers express a wish to see more discussions on safety issues of individual medicines in UR. The main intention of Uppsala Reports is not to discuss such issues however. The forum for this discussion is the WHO Pharmaceuticals Newsletter, issued by WHO headquarters. The WHO Collaborating Centre and Programme member countries use this vehicle to bring drug safety issues of concern to the attention of a global audience.

Uppsala Reports is often quoted in other fora, e.g. Scrip pharmaceutical news, particularly when controversial issues are discussed. Back issues are available as pdf downloads from the UMC website. We are looking forward to the next ten years and keeping in touch with readers and colleagues worldwide!

Priority: risk

Risk management continues to rise up the agenda in global pharmacovigilance, not least with the arrival of EU and US FDA risk management guidelines and the CIOMS VI Working Group recommendations[1] last year. In Thailand, in the third of a series of training courses, Thai regulators, physicians, pharmacists, academics and representatives of the pharmaceutical industry met in Bangkok early in March to discuss the latest thinking in risk management of medicines and its implications for the country.

Course teaching and organising team: Dr John McEwen (formerly of TGA Australia); Bruce Hugman (UMC); Dr Pravich Tanyasittisuntorn (Director of Clinical Research, Pfizer Thailand); Khun Wimon Suwankesawong, Head of Pharmacovigilance Unit, Adverse Product Reaction Monitoring Centre, Thai FDA; and APRMC pharmacists, Ms Pakawadee Sriphiromya, Ms Chootima Jameekornkul, Ms Sareeya Wechwithan, and Ms Rachada To-a-nan (in front). The event was opened by Prof. Dr. Pakdee Phothisiri, Secretary General, Thai FDA.

The two-day event was arranged jointly by the Thai Food and Drugs Administration, and PReMA, the Thai pharmaceutical industry association. It was led by Dr John McEwen, formerly of the Australian Therapeutic Goods Administration, with contributions from Bruce Hugman, *the* UMC's commmunications consultant. Last year, Dr Jürgen Beckmann (Germany), conducted the second in the series.

The broad sweep of topics included all aspects of the risk management process, including discussion of appropriate risk minimisation tools for Thailand, and a review of the latest international guidelines and publications.

Thailand is actively developing its regulatory régime, including the introduction of patient information leaflets to replace the current dual-purpose data sheet in medicines packs. Global and local manufacturers and CROs play an important part in the country's economy and healthcare and the collaboration underlying this event is part of a continuing national alliance.

1 Management of safety information from clinical trials; CIOMS 2005.

Balkans initiative

The WHO Regional Office for Europe and the European Union are joining forces in an effort to support reforms of the pharmaceutical sector in countries of Southeast Europe. Countries in this corner of Europe have either just become members of the EU, are official candidate countries, or have the ambition to join in the not too distant future. To create an opportunity for health authorities and drug regulatory agencies to exchange information and share experiences, WHO-EURO and EU organized the Southeast European Pharmaceutical Conference in Sarajevo, Bosnia-Herzegovina on 27–28 February, 2006. It was attended by over one hundred representatives of 11 countries in the region. The programme for the conference included a wide variety of issues including:

- The need for a national drug policy
- Legislation for the pharmaceutical sector
- Networks for pharmaceutical inspections and drug quality control
- Pharmacovigilance
- Approaches to drug pricing
- Achieving rational use of medicines
- Good pharmacy practice

the UMC was invited to present the WHO International Pharmacovigilance Network under the pharmacovigilance section and was represented by Sten Olsson. All countries participating in the conferences are already WHO Programme members except Albania, Bosnia-Herzegovina and Slovenia. It is hoped that after this conference the health officials present have a better understanding of the potential of collaboration and what the WHO Programme may offer.

Professor Bozidar Vrhovac speaking in Sarajevo.

A pioneer in the field of pharmacovigilance, Professor Bozidar Vrhovac from Zagreb, Croatia, made an important contribution to the conference by providing his personal views on how to achieve a rational use of medicines when resources are limited. Professor Vrhovac initiated ADR reporting in former Yugoslavia more than 30 years ago. His work is respected and admired not only within the territory of former Yugoslavia but around the world.

Pharmacovigilance, edgeways and edgewise

Shanthi Pal, QSM WHO HQ, writes

'Get a word in edgeways': contribute to a conversation when the dominant speaker pauses briefly (Concise Oxford Dictionary)

With less than 10 African countries in the WHO Programme, pharmacovigilance (PV) is very sparse in this colossal continent. But not all is gloom and doom: WHO, along with its partner organizations such as the UNAIDS, UNICEF and the Global Fund (GF), is making a concerted effort to improve access to essential medicines for high burden diseases such as malaria, TB and HIV/AIDS. Several training workshops to help countries write proposals to the GF for the procurement and supply-management (PSM) of these medicines are taking place. The GF strongly recommends that recipients of the fund implement mechanisms to monitor adverse drug reactions (ADRs) and that the cost of such activities may be included in the grant budget. This, then, could be the entry point for PV. Pharmacovigilance Centres, where already present, could help monitor ADRs to these medicines; and where there are no PV centres as yet, they could be launched from the PSM platform, with financial support from the GF.

Recently I had the good fortune of facilitating a PSM workshop organized by WHO, the Global Fund and other partners in Nairobi, Kenya. This workshop had three objectives:

1) to provide technical knowledge and skills in various areas of the PSM cycle;
2) to assist countries with approved GF proposals in the development of their PSM Plans;
3) to assist countries in developing the work-plan for direct in-country technical assistance.

Countries planning to write PSM Plans (Botswana, Eritrea, Ethiopia, Gambia, Ghana, Kenya, Lesotho, Malawi, Namibia, Zimbabwe) and those in the process of implementing the GF funded activities (Liberia, Somalia, South Africa, Sudan, Tanzania, Uganda, Zambia) attended this interactive workshop. First, different partner organizations and facilitators presented technical topics related to PSM planning and implementation. Later, some countries worked on implementation issues and others on developing their PSM Plans.

Few at the workshop had any real idea about PV and what WHO is doing in the area, an observation that does not surprise me any more. The workshop helped improve understanding of ADR issues, raise awareness about the WHO Programme for International Drug Monitoring, and identify how PSM plans could link up with national pharmacovigilance centres, the WHO and *the* UMC for ensuring the rational use of HIV, TB and malaria medicines. At the end of the workshop it was encouraging that many countries (Kenya, Liberia, Namibia, Tanzania and Zambia) had a structured pharmacovigilance plan in their proposals. That is the first step. Putting PV on the PSM agenda, however, is in itself an important move.

That we lack visibility is clear. But what is equally clear is that there is a growing awareness for pharmacovigilance, thanks to high-profile drug withdrawals and media hype. And there are all sorts of opportunities for us to 'infiltrate' the system and influence thinking towards PV – the Kenya workshop was one such opportunity. Countries should read the Guide to the Global Funds policies on procurement and supply management (http://www.theglobalfund.org/en/about/policies_guidelines/) and act on it, to promote PV activities. If budgeted for, PV would be but a small drop in the big sea of PSM events. But it is better than being absent altogether. Let us be creative, let us get in edgeways.

Non-drug interactions

Health Canada hosted an international symposium on Drug, Food, Natural Health Product Interactions chaired by Dr Brian C Foster (Senior Science Advisor Therapeutic Products Directorate and Adjunct Professor, Faculty of Medicine University of Ottawa) and Professor Edzard Ernst (Universities of Exeter and Plymouth, UK) on February 9 and 10, 2006. Opening remarks were by Mr Omer Boudreau, Director General, Therapeutic Products Directorate and Mr Neil Yeates, Assistant Deputy Minister, Health Products and Food Branch, Health Canada. The symposium brought together speakers and panellists from eight countries, and over 260 delegates representing academia, industry, health care professionals, consumer groups and patient advocacy organizations from across Canada. Three scientific sessions covered adverse effects due to interactions between drugs, foods and natural health products; mechanisms of action and means to evaluate the data; and international surveillance strategies.

Dr Mohamed Farah of *the* UMC was one of the speakers in the international surveillance session. His presentation highlighted that serious side-effects have occurred around the world due to mislabelling of herbal products. Problems arise in monitoring the safety of herbal medicines, and accurate identification of herbal products is problematic, but it is essential if concerns about the use of herbal medicines are to be understood. There are some procedures which need to be established at country level such as an inventory of most-used herbal products, recorded by scientific plant names that are understood all over the world. The principles of monitoring safety are the same for both conventional and herbal medicines, pharmacovigilance centres already receive reports about herbal medicines, and people use both types of medicines and even take them concurrently. He advocated collaboration between traditional healers, healthcare professionals, academics, industry and regulators, particularly in education for health care professionals and those involved in retail sale of these products. Combined use of these products may have risk of serious adverse events and those present suggested that all health care professionals must take responsibility to ensure that patients are aware of these risks.

Left to right Dr Peter de Smet, The Netherlands Dr Joanna Barnes, New Zealand Dr Adriane Fugh-Berman, United States Ms Cheng Leng Chan, Singapore Dr Mohamed Farah, Sweden Dr Jenna Griffiths, Canada

Medication errors

Kenneth Hartigan-Go, MD
Executive Director, The Zuellig Foundation

Introduction

Pharmacovigilance is about making drug products, as well as their use, safer. While the set-up for ADR monitoring catches product problems, it may also be a good system to detect if such a product was not being properly used. Medication error is one such problem. Lessons from medication error detection may help prevent future errors and protect health professionals and ultimately, their patients.

Generally, there is difficulty in obtaining the correct statistics on medication errors. Many of these errors are neither recognized nor reported. A study in the Archives of Internal Medicine based on data collected since 1999 stated that in the USA, more than 40 potentially harmful errors a day were found on average in hospitals. The most common mistake is giving medicines at the wrong time, completely omitting the dosage, and over-dosing. Errors occurred in one of five doses in a typical 300-bed hospital – an average of 2 errors per patient daily. Although not all dangerous, 7% of the errors were considered potentially harmful.

Causes of Medication Errors and some examples

Errors originating from the drug industry:

1. Mistakes can happen in the manufacture of medicines (e.g. wrong excipients)
2. Proper storage procedures not observed, making the drugs useless. Using expired tetracycline has been known to cause Fanconi's syndrome, for instance.
3. Failure to provide correct prescribing information: 10 mg/kg 6 hourly could mean 10 mg/kg per dose given every 6 hours, which is the wrong interpretation, or 10 mg/kg/day to be divided every 6 hours, which is correct.
4. Failure to do Post-Marketing Surveillance by manufacturers, and, if done, not communicating these data.
5. Misleading health and treatment claims by industry.

Errors arising from doctors' prescriptions:

1. Prescribing the wrong drug
2. Writing illegibly
3. Confusing the name of one drug with that of another
4. Prescribing or writing the wrong dose
5. Wrong route of administration as listed in the prescription
6. Prescribing the wrong formulation (eg is using slow release drugs inadvertently when the doctor meant ordinary tablets)
7. Prescribing the duration of treatment incorrectly
8. Prescribing wrongly for a given individual
9. Wrong identity of the patient
10. Failing to account for pre-existing disease
11. Failing to account for concurrent therapy
12. Prescribing with inadequate or incorrect instructions
13. Prescribing without informed consent of the patient
14. Off-label use of drugs.

Errors arising from pharmacists' dispensing

1. Dispensing errors – for example, giving 250 mg/5mL paracetamol instead of the prescribed 125 mg/5 mL preparation.
2. Misinterpreting doctor's prescription and failure to confirm with the prescriber.
3. Failure to provide advice to patients at the outlet. In poor resource countries, patients sometime purchase only a few tablets (they cannot afford a complete course). The pharmacist sells the medicines by cutting the medicine strips. As a result, expiry dates are sometimes no longer indicated on the purchased portion and information leaflets are rarely provided.

Errors arising from nurses' administration of drugs

1. Errors in drawing up and giving medicines
2. Wrong drug
3. Correct drug, wrong dose, dilution or formulation
4. Entraining air, particles or other contaminants with the drug
5. Errors in administration (interchanging IV, IM, intrathecal, oral, sublingual route)
6. Giving a drug outside or against currently accepted practice (off-label usage)
7. Wrong route, wrong site, wrong rate, wrong patient.

Errors arising from patient's drug intake:

1. Misunderstanding medication instructions
2. Poor patient compliance, not completing dosage regimen.
3. Drug paroxysm – when a patient takes a medicine but later becomes confused whether he actually took it and takes a second dose erroneously – not restricted to geriatric patients.

To counteract these possible errors, good prescribing practice guidelines are advocated:

- If it is possible to write the dose as a whole number, do so.
- If it is impossible or more confusing to write the dose as a whole number, ensure that a zero precedes the decimal point. Place the decimal point properly; a shift can mean 10 times more the intended dose, or can mean receiving only 10 percent of the intended dose. Use Gm for gram and gr for grain when specifying quantity. Best is to carefully spell out the whole word and dot the i. If grams are given instead of grains, the patient will receive 15 times the dose intended.
- Communicate clearly. Mobile phones and short message sending (texting) can lead to errors. Hospital should set up clear policies on telephone orders to prevent mistakes. Among doctors, nurses and pharmacists, when transmitting orders, clear pronunciation of medical terms and listening carefully can prevent mistakes of similar sounding drug names.
- Write a prescription clearly and give instructions to patients or their responsible companions. There was a case of an obese diabetic patient being managed with oral hypoglycemic medicine and instructed to decrease weight in a vague manner. The patient decided to skip breakfast as a 'diet control' measure but continued taking her medicine, leading to symptomatic hypoglycemia.

- Prescription should have all the essential information like dosage strength, the number of tablets, frequency of administration, route.
- Be conservative. Prescribe only when absolutely needed. Don't satisfy the whims of patients who request antibiotics to treat common colds.
- Know your patient's conditions well before prescribing drugs.
- Prescribe a medicine which you are thoroughly familiar with (adverse effects, contraindications, warnings). Don't be tempted to prescribe new medicines promoted aggressively by drug companies.
- If you want to prescribe a generic drug, it's better to indicate the particular company source you trust. Substitution of another generic product can mean lower drug levels (for drugs with serious bio-availability variations) and some countries have substandard generic products in the market.
- Avoid over-prescribing; this is costly and can lead to accidental overdose. Sometimes, an expired drug is unintentionally taken. Also, warn patients not to recommend an effective drug which they may have in excess at home to anyone else without consulting a health professional.
- Avoid polypharmacy. Although not all polypharmacy is bad when these medicines are actually needed, be attentive to those with potential for harmful interactions and be wary of drug-drug interactions.
- Spend time to educate a patient about the drug – when to take it, when to stop, what to expect (e.g., change in colour of urine?), how to recognize drug reactions and what to do, expiration dates, drug interactions and storage conditions.
- Some drugs when taken for a long time, should not be stopped abruptly (e.g. anticonvulsants, steroids, sedative hypnotics)
- Some drugs when taken long-term, may lead to drug dependence and abuse.
- Pay serious attention to the patient's history, such as records of hypersensitivity, allergies, idiosyncrasies to medicines, or medical conditions that are considered contraindications to drugs. Note these in patient's records and review when necessary before prescribing. Take note of the patient's occupation and possible risky interactions with his medicines.

Drug safety and rational drug use

Care must be exercised when handling drugs and treating patients. Negligence may lead to fatality, and commonly, a health professional may be charged with acts or omissions such as:

a. Not using available, objective and updated drug information and relying solely on a drug industry person for this information
b. Miscommunications on drug orders like poor penmanship, confusion between drug names, misuse of zeros and decimal points, wrong dosing units, and incorrect abbreviations
c. failure to obtain patient consent for the use of a drug in a manner not officially approved (off-label)
d. treatment of a condition with a drug not suitable for the condition
e. failure to note a history of drug hypersensitivity, concurrent medications, contraindicated medical conditions
f. failure to test patient for sensitivity to drugs like penicillin
g. improper injection techniques
h. failure to stop a medicine suspected to cause a reaction
i. failure to provide adequate intervention to counteract an adverse reaction
j. failure to communicate with patients
k. lack of correct labelling when drugs are repacked into smaller units.

By recognizing possible errors we can find ways to prevent them.

Examples from the Philippines

The Philippine Generic Drug Law of 1988 mandates that the labelling, prescription of drugs be done in generic or scientific nomenclature, with intention towards promotion of more affordable drugs and rational drug use.

The use of generic terms in prescription lessens chances of medication errors. Pharmacists validating prescriptions and checking important patient and drug details help prevent errors. Some case examples are presented here.

Mesulid vs Mellaril. The doctor prescribed Mesulid, without indicating nimesulide (the generic name), the pharmacist gave Mellaril (thioridazine) instead. Patient hospitalized.

Terbulin vs Theodur. A young asthmatic patient was given Theodur (a trade name product containing theophylline) by a doctor. On top of this, the doctor gave Terbulin, (a fixed dosed combination product trade name) mistakenly thinking that this is terbutaline alone but in fact contained theophylline as well. Patient went into theophylline toxicity, was hospitalized.

EMB vs EMBR. Tuberculosis patient was prescribed quadruple anti-Koch medications. The doctor abbreviated ethambutol as EMB but the patient was given instead the brand EMB a combination INH and ethambutol. Liver transaminases became elevated as the isoniazid dosage was more than necessary.

Unclear expiry dates. A patient had died due to a serious illness. Being attributed was the hospital staff using alleged expired medicine. The hospital misinterpreted the marked expiry date as month-day-year where in fact, it should have been read as day-month-year. The national drug regulatory agency failed to note, and standardize labelling as manufacturing and expiry dates presentation may vary from country to country.

Example from the Philippines – hospital

A call was received from a hospital nurse supervisor asking for help in investigating an incident.

An oncologist wrote instructions on the hospital chart for the IV administration of the oncolytic drug mesna (brand name Uromitexan), but the nurse mistook it for the respiratory solution also called mesna (brand name Mistabron). The respiratory solution meant for nebulization was injected intravenously for a total of 8 doses over 3 days until the error was discovered.

Patient was never told of the error by the attending physician and was, sent home on the same night. Some tests were ordered but these were never carried out. Drug industry help was sought on pharmaceutical physico-chemical information but they could not be contacted at the weekend.

The Philippines FDA was informed of the incident on Monday and they were surprised how they managed to register two drugs sharing the same name. The doctor, in following the Philippine Generics Act of 1988 mandating that the doctor should write the generic name of a prescribed drug, was unclear about his responsibility to indicate the specific product trade name.

The nurses (three shifts in three days) did not read the ampoule information prior to administration. The hospital pharmacist sent the ampoules to the floor without an accompanying box or product information leaflet. Patient could not be followed up.

Practical tips

Dangerous abbreviations that can occur in the pharmaceutical laboratory, pharmacies, hospital and clinical practice:

- D/C – as used in hospitals can mean discharge, discontinue or dilatation and curettage
- AU vs OU – because of spelling errors, can confuse both ears with both eyes.
- DPT vs dPT - A cocktail drug preparation used in hospitals known as Demerol, phenergan and thorazine can be confused with pediatric vaccines called diphtheria, pertussis, and tetanus.
- HCl vs KCl – again, H and K can be misread and instead of hydrochloric acid, potassium chloride is used.
- Per os vs left eye – os is sometimes used in hospital charts to mean opening, by mouth or by tube and can also mean the left eye.
- QD vs QID – once a day may be confused with four times a day.
- QN vs every hour qh – as letter N and H can be misread, every night is mistaken as every hour.
- QOD vs daily – this is particularly confusing when doctors make abbreviations misinterpreting every other day, or once every day.
- SC vs SL – C for cutaneous can be mistaken as L for sublingual.
- IU vs IV – international units as opposed to intravenous, for instance, insulin expressed in units to be given subcutaneously may be erroneously given as intravenous bolus.
- X3d vs three doses – the confusion here may be due to misinterpretation that a drug is given for 3 days as opposed to just three doses or three times in a day.
- Inderal40 vs Inderal 40 mg (mistaken 140 mg) - it is not unusual to have a wide range of dosing for propranolol therapy as in the management of hyperthyroid states but when there is a penmanship mistake – in this case, the absence of a space between the last letter and the subsequent number – a mistake can happen.

Conclusion

Medication errors can happen unintentionally. Health professionals should be vigilant in finding ways to prevent these errors. One way is to strengthen education and surveillance systems within the ADR reporting context. The role of pharmacovigilance centers can be expanded to address problems that occur in the clinical setting. Every health professional involved in the therapeutic chain should always question the decisions made by the ones before them (nurses and pharmacists question the prescriber on medications as prescribed etc.).

It would be serious to hear this from our patients: "Doctor, I prefer the disease to the side effects of the medicines you gave."

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Zuellig Foundation's think tank policy notes on the use of cellphone (text messaging or SMS) in hospitals 2002.

New permanent UMC staff

Last year **Johan Hopstadius** did his Masters thesis at *the* UMC analysing the adjusted IC estimate as a tool to control for confounding. He will work with research and development of new methods for data analysis. Besides studying physical engineering, he has previously run a small IT company working as consultant with both web and application development.

Anna Celén, Johan Hopstadius, Maja Östling

Johan is married and has one little daughter who occupies most of his time outside the office. During the winter he enjoys both downhill and cross-country skiing.

Anna Celén has a Master of Science in Pharmacy. Before *the* UMC she had working experience with 10 months military service in the Swedish Air Force and working as an au pair and studying German in Berlin.

In her spare time she is studying Spanish and Chinese, but she also does 'spinning' and plays the flute. She loves travelling and discovering different cultures. She has visited Taiwan three times and has a lot of friends there, enjoying the interesting culture, delicious food, beautiful scenery, great pop music and generous people.

Maja Östling is PA to the Centre Director and also Team support. Maja lives in a cosy 1930s apartment in central Uppsala with two Burmese cats and her boyfriend.

Her main studies were in photography, and she continues this interest as well as drawing, painting, and interior design – she also enjoys writing poems.

Ghana Centre visits Uppsala

The head of the Ghana Centre for Pharmacovigilance Dr Alex Dodoo and his deputy Ms Augustina Appiah-Danquah paid a one week working visit to *the* Uppsala Monitoring Centre in January 2006. The aim of the visit was to exchange ideas and experiences in pharmacovigilance and to hold discussions with UMC staff. The timing was intriguing since January is the coldest month in Uppsala and the Ghana team arrived from a temperature of +25C in Accra to -20C in beautiful Uppsala! However, the warmth of *the* UMC staff including the Director Ralph Edwards, Head of External Affairs Sten Olsson, Marie Lindquist, Cecilia Biriell and others ensured a pleasant stay and productive professional visit.

The Ghana team held discussions with several staff members who in turn gave hands on demonstrations on key tools such as the WHO Drug Dictionary, Vigibase Online, Vigisearch, WHO-ART and MedDRA. Discussions were also held on signal generation processing of ADR reports and the WHO Herbal Drug Dictionary. The team participated in an in-house seminar where VigiMine, a new tool for *the* UMC was demonstrated.

The mutual benefits of exchange visits to and from Uppsala by National Centres and UMC staff became evident and were discussed at length. Obviously with nearly 80 countries having full national centres, *the* UMC may not be able to host everybody at the same time, but it is worth exploring how best the staff from national centres may occasionally visit *the* UMC and vice versa.

Alex Dodoo and Augustina Appiah-Danquah

The experiences of the visit were unforgettable and will go a long way to strengthen the Ghana Centre as it seeks to become a regional centre in the training of pharmacovigilantes in Africa. The Ghana National Centre sees pharmacovigilance as a 'science with passion' and pursues it as such. With its staff strength recently increased to 19 (including part-timers) the Centre believes it can rightly fulfil some of the expectations of the discerning Ghanaian public including monitoring the safety of medicines used in public health programmes like malaria. The future looks bright!

Visitor from Seoul

Professor Byung-Joo Park, of the Department of Preventive Medicine, Seoul National University College of Medicine visited the UMC in mid-February. Specialist in Pharmaco-epidemiology and Clinical Epidemiology, he is a member of the International Society for Pharmaco-epidemiology since 1992, and a Co-Chair of the Global Development Committee.

The main purpose of his visit was to learn more about the WHO's role in ADR monitoring and pharmacovigilance, as well as the organization and activities of UMC, including ADR monitoring, data-mining process for detecting signals, risk assessment, management and communication.

Vigibase Online validated

The validation of Vigibase Online is now finished and version 3.0 of this sophisticated case report management system was released the 28th February 2006, complying with GxP requirements.

"The project has been very intense but we have gained a lot of experience to be used in future project as well in the continuous development of Vigibase Online", commented Magnus Wallberg (Manager of *the* UMC's Safety Reporting Support & Service and Systems Development). "As responsible systems developer I would like to thank the entire UMC team that has been involved in the project for a tremendous achievement."

the UMC is now planning for the next release of VBO in which the major new feature will be the possibility to use MedDRA as terminology instead of WHO-ART and ICD10, for those who need to use MedDRA (and who have a valid licence).

See report on pages 10-11 of UR32 for an interview with Magnus.

If you would like to know more about Vigibase Online please contact Magnus at the UMC.

Driving the message home

a note from Alex Dodoo

Various national centres are constantly using new and improved strategies to encourage ADR reporting. In Ghana, the National Centre has decided literally to drive home (and around) the message of medicine safety. Under a WHO-TDR grant 'Real-life study of chlorproguanil-dapsone (LAPDAP) and amodiaquine+artesunate in a resource-limited country Ghana', the Centre has acquired two vehicles for prospective intensive monitoring of patients following administration of chlorproguanil-dapsone and artesunate+ artesunate. The aim is to follow up on all patients taking these medicines regardless of whether they have any ADRs or not, in a bid to establish incidence rates and profiles of ADRs to these anti-malarial drugs. And one of the ways to promote this message? Print it on the cars and drive the message home!

the UMC and Uppsala University collaborate in training

For the first time the UMC has offered pharmacovigilance training with academic accreditation. Students passing previous UMC training courses, given in Uppsala and Canberra since 1993, have received a course diploma only which does not entitle to academic credits. Now the UMC has been invited to join forces with the Department of Toxicology, University of Uppsala, for a five week academic course on 'Adverse Reactions and Pharmacovigilance'. It was first offered as an optional course to pharmacy students in their 4th year and 14 students accepted to be test pilots for this new course which was given February – March 2006.

The first group of students on the ADR course.

The course integrates teaching on mechanisms of drug toxicity with methods in pharmacovigilance and risk communication. A mandatory individual task was to identify a recent safety warning or labelling change and investigate to what extent toxicology or clinical data was available in literature that might have allowed earlier identification of the particular risk. This new course was well received by students and will probably be repeated. Since it is given in English, Uppsala University is considering making the course open for applicants from other countries. If that will be the case we will come back with further information in a later issue of Uppsala Reports.

WHO Drug Dictionary Enhanced hits the million mark

the UMC Products & Services are striving to make the WHO dictionaries high quality products with timely releases and optimal support functions. To be able to increase the coverage in a larger number of countries and get fast access to information about new releases *the* UMC is collaborating with IMS Health. The result of this collaboration is called WHO Drug Dictionary Enhanced which contains data from both the WHO Drug Dictionary and the IMS Health data. It is produced in the same formats and with the same principles as the previous WHO Drug Dictionary.

The collaboration project started within *the* UMC Products & Services in 2004. At the end of the project more than 15 people from both of the divisions within UMC were involved. The project team have worked intensively to analyze, map and verify the IMS data, and to import the data into the WHO Drug Dictionary Enhanced structure. A lot of effort has been put into the quality assurance of the dictionary; the large amount of data has been a big challenge for both technicians and pharmacists. The data in the dictionary has been released at four intervals over the last year. The fourth release of the WHO Drug Dictionary Enhanced, released March 1 2006, contains more than 1 million Medicinal Product IDs and nearly 180,000 unique trade names from 95 countries (including the IMS data from 66 countries).

It has been a learning year; the ambition was to computerize most of the work, as we did, but still a lot of manual effort was needed to verify and to validate the trade names from IMS, as these often appeared shortened. We have got a lot of experience how medicinal products are spread over the world and which substance/combinations are the most common. A lot of trade names are repeated exactly in different countries and a handful of substances/combinations such as Paracetamol, Sulfamethoxazole/Trimethoprim, Ibuprofen, Amoxicillin trihydrate and Diclofenac sodium have each almost 1,000 trade names represented in the dictionary.

The project is now translating into a maintainance operation where the collaboration with IMS continues in quarterly updates of IMS data to be included in the WHO Drug Dictionary Enhanced.
Statistics based upon product information from the WHO Drug Dictionary Enhanced release March 1, 2006;

Type/format	number of medicinal product records in C format	number of Drug records in B1 format	number of Drug records in B2 format
WHO Drug Dictionary	144,476	119,074	60,559
WHO Drug Dictionary Enhanced	1,066,042	584,168	180,446

The top 7 countries for medicinal products;

Country	Number of Medicinalproduct_ids
USA	72,577
PRI	51,480
IND	40,526
DEU	37,026
JPN	35,643
CHN	28,565
GBR	23,692

The top 7 - list of trade names;

Country	Number of trade names
JPN	15,257
IND	14,419
DEU	10,662
USA	9,092
KOR	7,753
TWN	7,524
GBR	7,345

The top 7 - list of substances/combinations;

Country	Number of trade names
DEU	24,537
USA	23,373
IND	20,347
JPN	18,527
CHN	15,419
GBR	14,159
TWN	12,694

Meet the team

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

June 18-22
42nd DIA Annual Meeting, Philadelphia, PA, USA

August 24-27
22nd International Conference on Pharmacoepidemiology (ISPE) & Therapeutic Risk Management, Lisbon, Portugal

October 8-11
The Society for Clinical Data Management (SCDM), Wyndham Palace Resort & Spa, Orlando, Florida, USA

Nike, Sven and Malin discussing the IMS data and how to improve the import functions.

Need help?

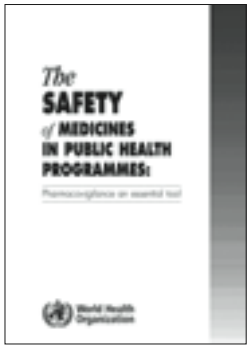
If you have any queries about WHO-DD, or need further information about your current subscription or how to upgrade it, do contact *the* UMC Products & Services.

You can e-mail:
drugdictionary@umc-products.com for comments about the WHO-DD, WHO-DD Enhanced, corrections and additions, and katarina.hansson@umc-products. com for queries about your subscription.

NEW PUBLICATIONS

Safety of medicines in public health programmes – pharmacovigilance an essential tool

The Quality Assurance and Safety of Medicines team of the World Health Organization (WHO) continues its series of publications on safety monitoring of medicinal products. This text on pharmacovigilance in public health programmes was developed in consultation with the WHO Collaborating Centre for International Drug Monitoring and the national pharmacovigilance centres participating in the WHO Programme for International Drug Monitoring.



The WHO has historically played a seminal and vital role in promoting the safety of medicinal products as a clinical and public health issue. An even greater challenge lies ahead — those countries that do not have the necessary facilities, expertise and resources for pharmacovigilance arguably need them the most. In working to achieve this it will be important that the traditional division between medicine safety on the one hand and public health on the other should cease to exist. Technological advances have been made in information capture, storage and retrieval. Equally there are now improved systems and resources for financing public health and medicine safety initiatives. Specialization in medicine safety, and a growing awareness of the importance to the public good of medicines that are safe and rationally used, in addition to their efficacy and good quality, should make these objectives realizable.

In any public health programme, a well-integrated pharmacovigilance system must ultimately result in cost savings through early recognition and management of these risks. The development of pharmacovigilance within a public health programme should be seen as an obligatory investment in the future public health of the territory.

This document demonstrates that pharmacovigilance can and should be an integral part of every public health programme that uses medicines in order to optimize the use of scarce health resources and prevent potential tragedies. Pharmacovigilance may be crucial to the success of such programmes. The purpose of this report is to explain why this integration needs to happen and how it can be done.

CONTENTS

Pharmacovigilance book published in Serbia

A book devoted to adverse reactions and various aspects of pharmacovigilance was recently published by the Pharmaceutical Faculty of Belgrade. The book, entitled 'Farmakovigilancia i bezbedna primena lekova' (ISBN 86-80263-34-6) was edited by Branka Terzić, Draginja And'elković, Ronald Meyboom and Milan Stanulović. The 150-page publication has 20 chapters focusing on different aspects of drug toxicity including mechanisms of action, methods of study and clinical manifestations in various organ systems. All chapters have an English summary.

Pharmacovigilance of Anti-Malarials in Ghana – A primer for healthcare professionals

Published in February 2006

A handy 24-page manual, very direct and practical, with several short exercises for the general reader to try out. It covers:

- Definitions of drug safety terms
- Background to pharmacovigilance
- Classification of ADRs
- Pre-disposing factors for ADRs
- Pharmacovigilance in Ghana
- Reporting and prevention of ADRs
- Copies may be obtained from
- National Centre for
- Pharmacovigilance, CTCPT

University of Ghana Medical School
Korle-Bu Teaching Hospital
PO Box GP 4236
Accra, Ghana

Levads farmakovigilancē

A 128-page illustrated book has been produced in Latvian setting out the background to and need for pharmaco-vigilance, articles on the issues of drug safety in Latvia and descriptions of clinical problems in relation to pharmacovigilance.

Enquiries to the Latvian national centre.

Correction

We gave an incorrect postcode in the address to write for 'Feeling Better Doctor' (UR32 p20); the UK postcode should be SO33 2BX. Apologies.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
10-12 April 2006	27eme journées de pharmacovigilance ISPE Mid-Year Meeting	Montpellier, France	Secrétariat de la Société Française de Pharmacologie Tel: +33 2 35 14 86 04 Fax : +33 2 35 14 86 09 E-mail: secretariat@pharmacol-fr.org
24-25 April 2006	Adverse Event Reporting and Pharmacovigilance	Rockville, Maryland, USA	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
24-25 April 2006	Pharmacovigilance of herbal medicines: Current state and future directions	London, UK	IIR Tel: +44 (0)20 7915 5055 E-mail: registration@conferences.com www.iir-events.com
27-28 April 2006	Back to Basics in Pharmacovigilance	London, UK	Dr John Clements, Science Secretary Royal Pharmaceutical Society of Great Britain Fax: 020 7572 2506 E-mail: science@rpsgb.org
27-28 April 2006	Compliance in Pharmacovigilance and the Role of the EU Qualified Person. US & EU Requirements including Volume 9A highlights.	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
11-12 May 2006	DIA 42nd Annual Meeting	London, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
18-22 June 2006	Risk-Benefit Assessment in Pharmacovigilance	Philadelphia, Pennsylvania, USA	DIA Fax: +1 215 442 6199 www.diahome.org
5-6 July 2006	Advanced GCP (Pharmacovigilance) Course	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
28 July 2006	22nd International Conference on Pharmacoepidemiology & Therapeutic	Singapore	National University of Singapore Tel: +65 6516 3023 Fax: +65 6778 5743 E-mail: kamaliah@nus.edu.sg
24-27 August 2006	Risk Management	Lisbon, Portugal	International Society for Pharmacoepidemiology Tel: +1 (301) 718 6500 Fax: +1 (301) 656 0989 E-mail: ispe@paimgmt.com
6-7 September 2006	Critical Appraisal of Medical and Scientific Papers	Southampton, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
28-29 September 2006	1st European Conference on Risk Management Planning and Pharmacovigilance Safety Specifications	London, UK	DSRU Tel: +44 (0)23 8040 8621 Fax: +44 (0)23 8040 8605 E-mail: jan.phillips@dsru.org
11-13 October 2006	International Society of Pharmacovigilance (ISoP) Annual Scientific Meeting. Pre-conference training courses.	Liège, Belgium	International Society of Pharmacovigilance E-mail: info@isop2006.org www.isop2006.org
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
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
	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/

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Please contribute!

We aim to make Uppsala Reports an interesting and valuable communication for anyone working in or interested by drug safety issues and the WHO Programme for International Drug Monitoring.

If you would like to contribute news or a longer article or feature to Uppsala Reports, please get in touch with Sten Olsson or Geoffrey Bowring (e-mail instructions below). We are always happy to hear from readers wherever you are in the world and whatever your part in safety of medicines or public health.

If you have any other comments about the publication, please let us know.

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