

MUR21

UPPSALA REPORTS JANUARY 2003

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

**On-line reporting to
Uppsala**

**Reports from meetings in
Amsterdam**

**UMC training course in
Australia**

Data input: quality control

**70th country joins WHO
Programme!**



DIRECTOR'S MESSAGE



I have been travelling recently to Ghana, South Africa, Australia and New Zealand. In each place many instructive discussions took place. I would like to tell you about two of these.

In Ghana we talked about planning, particularly long-term planning. It was suggested that all national centres should have a rolling four-year plan, which is updated annually. WHO/UMC already works on this basis. It would be very productive for all national centres to come to the Annual Meeting to share their plans. Not only could Member Countries learn from each other's strategic aims, but it would also enable all plans to be incorporated into a WHO Programme rolling four-year plan, clearly charting the longer-term aims of international pharmacovigilance. What do you think? Why haven't we done this before?

In New Zealand, the Intensive Medicines Monitoring Programme has very large cohorts of women using the Multiload IUCD and the progestogen loaded IUCD 'Mirena'. These cohorts are unique and findings from them will be very interesting. Several papers are in the pipeline.

Otago University not only hosts the Medicines Adverse Reaction Centre, but it is in very close association with the Dept. of Social and Preventative Medicine under Prof. David Skegg. The reputation of this department for studies on the oral contraceptive, HRT and various health matters is well known internationally.

Our discussions in New Zealand covered all kinds of issues relating to women and drugs. What about pregnancy and drug effects? Lactation? Should any new drug be subject to international assessment for its effects on the foetus, given that unintended exposure in early pregnancy is almost sure to occur? How would we do this? Should clinical trials include women? It would be very interesting to hear your views on this.

Overall, I was left with the feeling that we knew much too little about drug effects in half the world's population!

The trip home took about 50 hours. This was due to the complex flight out, which meant only certain sensibly-priced options were open to me on the way back. I hate travel because of the hassles, enforced immobility and invasion of personal space one has to suffer, but the trip gave me time to reconfirm my confidence about how much we can achieve together, if only we can negotiate and overcome the man-made obstacles.

Perhaps it will be better in the New Year!

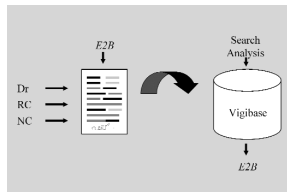
Finally, a word of thanks to all those who attended the Annual Meeting in Amsterdam and *the* WHO/UMC training course at TGA in Canberra and made them such productive and enjoyable occasions (both reported elsewhere in this edition of Uppsala Reports). And thanks, too, to our hosts in both countries who managed everything so well and looked after us so generously.

A very happy and successful 2003 to you all!

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

5
Vigibase on-line: introducing an on-line reporting system from doctor to National Centre to UMC



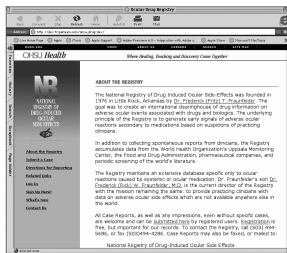
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Extended WHO family

We are very pleased to announce that the WHO International Drug Monitoring Programme has now reached the level of 70 active participating countries. The 70th country to be formally admitted was Jordan. Contact person at the National Centre in Jordan is Ms Nancy Ghabboun, who attended the National Centres meeting in Dunedin in 2001 and the pharmacovigilance training course in Canberra in 2002. (She is interviewed on page 12 in this edition of Uppsala Reports).

Contact details are:
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 P.O. Box 86, AMMAN
 Tel and fax +962-6-5660 028;
 E-mail: drugdirct@index.com.jo

Other countries formally joining the WHO pharmacovigilance network during 2002 were Peru, Latvia, Ukraine and Guatemala. Since the turn of the century 14 countries in total have entered the International Programme.

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Summary

WHO plays a critical role in updating the lists of controlled drugs; decisions on addition to or removal from lists are taken at the United Nations Commission on Narcotic Drugs. Epidemiological data are very scarce, and despite recent methodological advancements, actual abuse is often hard to predict based only on laboratory test results. In recognition of their utility, abuse-related ADR data from the UMC have in recent years always been included in the data set compiled by the WHO Secretariat for assessment of medicinal psychoactive substances. In some instances, such data was crucial to the abuse liability assessment.

Conceptual confusion about terminology is common, and affects the process of case detection and reporting, as well as data interpretation. The most frequent confusion is the relationship between withdrawal syndrome and drug dependence.

Using UMC data for the international drug control system

Introduction

Drugs of abuse are controlled internationally by the United Nations. Within this system, WHO plays a critical role in updating the lists of controlled drugs in response to the changing patterns of drug abuse. It assesses the abuse liability of psychoactive substances and proposes their addition to or removal from these lists or their transfer from one list to another. Final decisions are taken by voting at the United Nations Commission on Narcotic Drugs. Through this decision-making mechanism, the number of narcotic drugs and psychotropic substances under international control has increased with time, to over 200 by the end of 2000.

Scarcity of epidemiological data

Abuse liability assessment requires relevant data. Despite recent methodological advancements in laboratory studies, actual abuse is often hard to predict based only on laboratory test results in both animals and humans. Epidemiological data, however, are very scarce. Only a small number of countries with adequate resources have a data collection system in place concerning the abuse of drugs by drug abusers seeking treatment. Surveys concerning the abuse of drugs by the general population are also costly and they are rarely undertaken in countries with resource constraints. Police statistics (more widely available), also provide some indication about the extent of illicit availability of drugs. However, they don't exist unless the drug is already subject to legal control.

Utility of ADR data

In the light of the general scarcity of epidemiological data, the utility of abuse-related ADR data is quite significant. The WHO Adverse Reaction Terminology (WHO-ART) contains the following abuse-related ADR terms: drug abuse; drug dependence; withdrawal syndrome; withdrawal syndrome, neonatal. In addition, there are several closely related terms like: drug maladministration; drug habit; drug habituating. The data collection system is sensitive enough to detect dependence liability in therapeutic use, though it may not pick up genuine abuse 'on the street'.

In recognition of their utility, abuse-related ADR data from UMC have in recent years always been included in the data set compiled by the WHO Secretariat for the assessment of medicinal psychoactive substances by the Expert Committee on Drug Dependence. In some instances, such data played a critical role in the abuse liability assessment by the Expert Committee.

One example is zolpidem, for which exposure data (sales statistics) were also available from its manufacturer, which enabled a rough comparison of zolpidem to be made with benzodiazepine hypnotics with respect to reporting rates of withdrawal, dependence and abuse.

Understanding terms

Although abuse-related ADR data are very useful for the assessment of the risk of dependence and abuse in medical use, there are a few constraints. For example, conceptual confusion about terminology is still rather common, affecting the process of case detection and reporting, as well as data interpretation and communication. The most frequent of such confusions is about the relationship between [withdrawal syndrome](#) and [drug dependence](#). This problem has emerged in the course of discussions on how to interpret the significant numbers of withdrawal syndrome cases and the smaller numbers of drug dependence cases reported for SSRIs. The modern definition of drug dependence requires neither withdrawal nor tolerance, since an individual can become dependent on a drug without necessarily developing tolerance or demonstrating withdrawal symptoms upon discontinuation of the drug. However, excessive emphasis on this can lead to the opposite misconception: that withdrawal is unrelated to dependence. When an individual has difficulty in managing the need for repeated doses of the drug to feel good or to avoid feeling bad, the person is considered 'dependent' on the drug. Therefore, severe withdrawal can lead to dependence, but not always - this (mistaken) notion is widespread. The use of a different term [discontinuation syndrome](#) to replace the conventional expression [withdrawal syndrome](#) is adding more confusion to this debate. However, whether the reactions are called discontinuation syndrome or withdrawal syndrome, the terminology would have no influence on the person's need for repeated doses of the drug. Rather, it is the severity of the reactions to drug discontinuation that will determine the need for repeating the doses of the drug to avoid feeling bad. This example indicates the need for continued efforts to clarify the meaning of key terms used in pharmacovigilance.



Tokuo YOSHIDA

Quality Assurance and Safety:
Medicines

World Health Organization, Geneva

New software solution for pharmacovigilance centres

Software is now available from *the* UMC for pharmacovigilance centres that are in need of a modern system for management of adverse reaction reports. Over the past year *the* UMC has been collaborating with the Swiss medicines agency, Swissmedic (IKS), on the challenge of improving ADR reporting and feedback in the age of the internet.

The web has made possible the creation of a channel for improved communication between reporting and prescribing physicians and a pharmacovigilance centre. Swissmedic recently needed to upgrade their system, but instead of building something completely new *the* UMC has built a system on top of the new UMC database Vigibase. The system accesses Vigibase over the internet, so no local installations are required, and thus no licenses of database systems and servers. Reports can be entered and assessed via a secure internet connection by the doctor reporting an ADR. The report is then accessed by assessors from a regional centre and the national centre.

The development with the Swiss agency has guaranteed a solution that solves the basic needs of a national centre, and it can be developed to add new useful functionality:

- Vigibase on-line includes an advanced security system that makes it available only for authorised personnel, to avoid unauthorised access to data and the risk of hacking.
- The system can be set up to allow on-line ADR reporting by physicians. The physician enters data in structured format and in some free-texts *Fig 1*. A number of tools are available to allow easy entry and to guarantee data coherence.
- The report is made available to the first level of assessment – in the Swiss case a regional centre. The regional assessor has access to the same interfaces as the reporting physicians with some additions *Fig 2*.
- The report is routed to final assessment at the national agency, where an assessor can make a final validation of the report *Fig 3*.
- When the report is completed it is downloaded to the Vigibase database where it will be available for searching by the reporting centre and all other National Centres. It will also be available for statistical analysis by *the* UMC *Fig 4*.

Potential for different national centres

This innovative and seamless system can be copied or adapted for other National Centres. It can be developed further by adding additional tools, and this development can be shared by the National Centres that want to use the additional modules. Potential add-ons to facilitate the use of UMC services such as Signal document, Combinations database are planned.

A generic project plan for the implementation of Vigibase on-line at a pharmacovigilance centre is available. This gives an idea of what *the* UMC can offer and what is required by a National Centre. Among things to be discussed are the reporting processes in the country, whether physicians should access the system, and if there is a system of regional centres. The system can be implemented with or without all user types; it can even be implemented with on-line patient reporting. It is intended to be made available also as low-cost product, compatible with international standards, for developing countries.

If the pharmaceutical companies are primary reporters in a country, that can also be supported if the incoming reports are in E2B format. Medicinal product information from a country can also be incorporated to guarantee that a reporting physician can find the right product when reporting.

We are hoping that many National Centres will consider using Vigibase on-line, and that it will help Centres to focus on what they are best at – analysing ADR data.

If you have any comments or if you want more information, or access to a demo installation, please contact:

Daniel von Sydow
Project Co-ordinator Business Development
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IKS (Vigibase on-line)

Path of ADR report

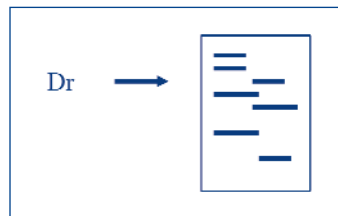


Figure 1: Physician enters report

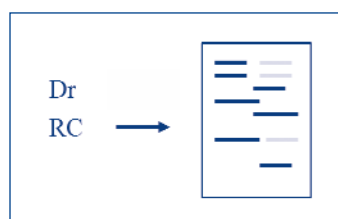


Figure 2: Regional Centre then adds information

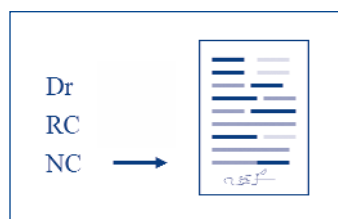


Figure 3: National Centre completes report then signs off



Figure 4: report enters the WHO database and is available for searching

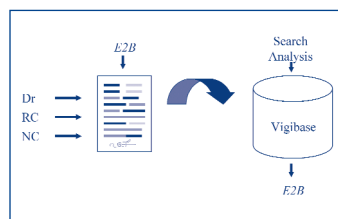


Figure 5: E2B format throughout



Dr Asamoah-Baah

Positive 25th WHO Programme meeting

The Netherlands was one of the ten founding members of the WHO International Drug Monitoring Programme in 1968. Dutch drug safety experts have made very important contributions over the years to the development of pharmacovigilance in general and the WHO Programme in particular and still do. When the Dutch Government and the pharmacovigilance foundation LAREB invited WHO to celebrate the silver jubilee annual meeting of representatives of National Centres in Amsterdam in 2002, it was accepted with great satisfaction.

The meeting was held on 14 - 16 October at the Royal Tropical Institute, which proved to offer aesthetically very attractive facilities, practical for participants and within easy reach of central Amsterdam. The organizing team, under the leadership of Kees van Grootheest, spared no efforts to give meeting participants and speakers administrative support and guidance, allowing them to concentrate on the professional content of the meeting. There were more than 100 participants, representing some 45 different countries which makes this 25th anniversary one of the biggest annual meetings ever.

The meeting was opened by Jonathan Quick, Director of Department of Essential Drugs & Medicines Policy, WHO. In his opening speech he reviewed the development of adverse drug reaction monitoring since the 1960s and particularly the very positive and dynamic role played by the WHO Programme since the first annual meeting of National Centres in 1978. Reports of recent progress were also given by Lembit Rõgo and Mary Couper from Quality & Safety of Medicines, WHO and Ralph Edwards and Marie Lindquist of the UMC. Later, the Executive Director of Health Technology & Pharmaceuticals, WHO, Anarfi Asamoah-Baah, gave a keynote address, speaking about the importance of pharmacovigilance in developing countries. Dr Asamoah-Baah stayed for the rest of the meeting and contributed much across a range of discussions.

Other highlights of the professional programme were:

1. A session on links between pharmacovigilance and toxicovigilance. Presentations were made from the International Programme on Chemical Safety, IPCS (Lesley Onyon) and experience of integrating poison information and pharmacovigilance was provided from France (C Kreft-Jais), Morocco (R Souleymani-Becheikh), Tanzania (M Masanja) and Uruguay (M Burger).

2. A session on pharmacovigilance and the Essential Drugs Concept. Chris van Boxtel spoke about the safety of the WHO Essential Drugs, Marcus Reidenberg presented his view on the need to tailor therapy to the individual and Thomas Moore discussed the pros and cons of combination therapy.
3. Parallel working groups focussing on four different subjects:
 - monitoring of herbal medicines
 - current issues in safety monitoring of vaccines
 - drug withdrawals - when, what, why and how?
 - developments at the UMC - Vigimed e-mail information exchange and the Signal review process
4. Discussions of 'Drugs of Current Interest'. Delegates presented 20 different drug related problems for discussion and information exchange.
5. Recent developments on the international scene with relevance to pharmacovigilance were presented: Pharmacovigilance in the ICH process was presented by Kaname Kanai, Japan, developments at the European Union by Panos Tsintis, EMEA, and conclusions from the International Conference of Drug Regulatory Agencies (ICDRA) by Jürgen Beckman, Germany. Juhana Idänpään-Heikkilä gave an interim report from the CIOMS VI working party on 'Collecting, reporting and assessment of safety information from clinical trials', and Chris Turner, Canada, reported about MedDRA developments.

Much discussion evolved after the presentations about recent international developments outside the WHO Programme. Many delegates felt that there are several initiatives taking place which overlap with, duplicate or even threaten the work of the WHO Drug Monitoring Programme. The discussion led to the meeting adopting the resolution printed on the left of this page.

WHO Programme resolution

This 25th Annual Meeting of National Centres Participating in the WHO Programme for International Drug Monitoring recognises that the production of a Drug Dictionary by the European Commission will severely compromise the activities of the Uppsala Monitoring Centre (UMC). This unilateral development of an alternative system places the WHO Programme for International Drug Monitoring in jeopardy because pharmacovigilance in the majority of countries in the world, representing the greater part of the global population, is dependent on the collaborative support of the UMC and WHO. We therefore strongly express our opinion that the European Commission should not proceed with the development of a new Drug Dictionary in the absence of active collaboration with the UMC/WHO.

Passed with acclamation 16 October

... followed by a packed ISoP meeting

The WHO meeting was followed, in the same venue, by the Annual Meeting of ISoP (International Society of Pharmacovigilance). Attended by over 350 delegates, it included many interesting and stimulating presentations and discussions.

For the first time a joint afternoon was organized for delegates of both WHO and ISoP meetings. This session was devoted to a report of the main issues of the WHO meeting and recent developments on the international pharmacovigilance scene.

Of particular interest, the ISoP General Assembly included a discussion of how the Society might assist those affected by supra national bodies such as the International Committee on Harmonization (ICH). Following the Combined Session with the WHO meeting on 16th October, Ralph Edwards introduced an open session in the ISoP Assembly about supra-national organisations, and the effects their activities and decisions have on those working in pharmacovigilance, particularly in industry.

Suggestions for addressing this issue included:

- a facility within ISoP meetings to review ICH decisions or other ways of brain-storming problems
- a discussion group at the ISoP website
- an e-mail discussion group for ISoP members, along with a repository of FAQs on, for example, interpreting E2B, at the ISoP website.

The Society will discuss the matter further at its Executive Committee; the Society President, Ralph Edwards, affirmed that the Society could offer a forum and put forward ideas, and he would report back on how concerns could be dealt with.

Three posters covering very different aspects of pharmacovigilance activities around the world, were jointly acknowledged. The three were:

- The Brighton Collaboration (USA and France)
- Selective serotonergic vasoconstrictors in suspected association with pain activation (The Netherlands and New Zealand)
- Internet government information about recall of medicines (Brazil).

A special conference supplement of the journal *Pharmacoepidemiology and Drug Safety* was published by Wiley (Vol 11 Sup 2 October 2002).

The social programme of the WHO meeting included a boat tour on the canals of Amsterdam and a jubilee dinner in the Council room of Hotel The Grand, a truly grandiose ambience.

We are indebted to the organizing committee for ensuring that all facilities needed for an enjoyable and successful meeting were in place and functioning to everybody's satisfaction. Amsterdam is a unique city with an international atmosphere offering many attractions, including some of the most impressive art museums in the world. Going there for a professional conference is quite frustrating since there is too little time to enjoy the natural and cultural attractions. There are many reasons for coming back, however.

Report from Sten Olsson



'Refreshments and posters in Amsterdam

Herbal Guidelines

Safety Monitoring and Pharmacovigilance of Herbal Medicines

Just prior to the 25th WHO International Drug Monitoring Programme meeting in Amsterdam last October, there was another international get-together. Representatives from regulatory and academic backgrounds around the globe met for two days to discuss the preparation of Guidelines on Safety Monitoring and Pharmacovigilance of Herbal medicines. The chair was David Coulter (New Zealand) and Mohamed Farah represented the UMC.

The intention is for a document to be published by the Department of Essential Drugs and Medicines Policy (EDM) at WHO in Geneva. The project is being led by Dr Xiaorui Zhang and the Traditional Medicines team within EDM, and involves input from experts around the world.

India in 2003

The 2003 meeting of countries participating in the WHO Programme for International Drug Monitoring will take place in the capital of India, Delhi. The Indian national pharmacovigilance centre and the All India Institute for Medical Sciences (AIIMS) will host the event from 8-10 December 2003.

PROFILE OF DAVID FINNEY

Most people working in pharmacovigilance today are aware of the modern beginnings of the discipline during the 1960s. One of the principal players in the pioneering years of pharmacovigilance was David Finney, who was an honoured guest at the WHO Programme and International Society of Pharmacovigilance (ISoP) meetings in Amsterdam last October. He is well-known as the author of scientific papers and books on statistical methods. Emeritus Professor of Statistics at the University of Edinburgh, he can reflect on how the WHO Programme and national initiatives in the United Kingdom came about, and what they mean for today's pharmacovigilantes. As well as presenting an absorbing paper 'From Thalidomide to Pharmacovigilance' in Amsterdam he also talked to members of *the Uppsala team*.



Marie Lindquist (UMC) talks with David Finney at the WHO meeting in Amsterdam

Pioneer in Pharmacovigilance

Background in Statistics

David Finney was born in 1917, read mathematics at Clare College, Cambridge, and worked as a statistician at Rothamsted Experimental Station during 1939-45. After the war he became Lecturer in the Design and Analysis of Scientific Experiment, University of Oxford until 1954. He then became Reader in Statistics (later Professor), at the University of Aberdeen, Scotland, and Director of the UK Agricultural Research Council's Unit of Statistics (until 1966 in Aberdeen, afterwards at the University of Edinburgh), retiring in 1984. It was during the 1960s that he became involved in the first international efforts for drug safety.

Seeds sown in Harvard

From September 1962 to August 1963, David Finney spent time in the Statistics Department of Harvard University in the USA. His immediate research concern was a large computational problem related to plant breeding. However, during his stay he enjoyed the hospitality of the Department of Preventive Medicine. David D Rutstein, then Professor of Preventive Medicine told his guest that he hoped he might have ideas on how statisticians could help to detect early warnings and so prevent recurrence of disasters like the thalidomide crisis that was then alarming the medical world.

Finney read the reports from McBride in Sydney and Lenx in Hamburg. He visited Frances Kelsey of FDA, whose suspicions had ensured that thalidomide never became a disaster in the USA. He put his preliminary suggestions in a short paper; and with encouragement from Rutstein, Louis Lasagna and others, developed his ideas in greater detail and prepared a more formal memorandum.

Clinical research was already aiming to reach the standards of design and objectivity that were expected in non-medical biological research. Finney could see that data collectable on adverse reactions would never have the objectivity, freedom from bias, and mutual independence that, as an experienced biometrician, he expected in well-designed experiments. This was a step towards his firmly-held belief that when faced with a problem of vital importance to public health and welfare, and despite severe imperfections in the only available data, a statistician may have an ethical duty to make use of skills he possesses for extracting usable information.

UK reactions

In 1963, the UK Ministry of Health asked Professor Sir Derrick Dunlop to head a new agency, the Committee on Safety of Drugs (CSD), to advise on the protection

of the community against adverse reactions to therapeutic drugs. From among medical scientists, Dunlop assembled sub-committees to work as volunteers, with a central medical and administrative staff. Dunlop, aware of his memorandum, asked Finney to join the Sub-Committee on Adverse Reactions. So began his period of over thirty years of fascinated involvement in this subject.

The Ministry of Health had written to every British doctor urging alertness to any 'untoward condition in a patient which might be the result of drug treatment'. Whether prescribed by a physician or purchased over the counter, Dunlop hoped that spontaneously submitted reports would come to the CSD for study by the Sub-Committee. Doctors began to send in reports, and in 1964 Dunlop appointed Dr Bill Inman as a Medical Officer to the CSD Secretariat, with special responsibilities in respect of adverse reactions.

International spread

From the start, Finney believed that, because the drug industry was world wide, effective action for safety needed international co-ordination. In 1963, he visited Geneva to talk with Dr Hans H Halbach of WHO, who was then facing a novel and difficult problem. In 1962, as a consequence of the thalidomide tragedy, the Member States had requested that WHO should initiate an international programme for exchanging information on safety and efficacy of drugs.

The next year saw the first of many small meetings to examine the development of international standardised reporting and dissemination of information. Most were held in Geneva, others in Washington and Honolulu. Relevant experts with national responsibilities for drug safety met for intensive but constructive discussion about ways of creating a viable international centre. Almost all his memories of WHO in the 1960s to 1970s are pleasant; although he sometimes found an excess of bureaucracy, the atmosphere was always friendly and helpful with excellent facilities for intensive meetings and a highly competent and hard-working secretarial support staff.

Through these meetings, input from those operating monitoring programmes in their own countries produced advice for Halbach on creating a WHO co-ordinating centre. Following a feasibility trial in Virginia, USA, this centre was moved in 1970 to Geneva. In 1978, WHO accepted an invitation from the Swedish Government to move the centre to Uppsala: thus was created *the Uppsala Monitoring Centre*.

Data and events

From his time at Harvard, David Finney had sensed the need for language and terminology that would assist objective discussion of evidence. It was natural for a statistician to be unhappy with the subjectivity of reports that originated in suspicion, not fact. He therefore proposed that more informative data would be obtained if a cohort of patients beginning to receive a nominated drug could be identified and their subsequent medical history recorded in respect of events experienced. This suggestion may have been the first introduction of the term 'event' to pharmacovigilantes. He also stressed the need to keep careful account of how cases or patients suffering from adverse events were ascertained for inclusion in monitoring files.

Professor Garth McQueen took his idea further of defining a cohort as consisting of all persons for whom a named drug is prescribed and then seeking to record subsequent event history for each of them. McQueen established the Intensified Adverse Drug Reaction Reporting Scheme in New Zealand in April 1977, which is now called the Intensive Medicines Monitoring Programme (IMMP), and directed by David Coulter, who has just celebrated 25 years involvement with the IMMP. A little later, Bill Inman developed a similar scheme – to become known as Prescription-Event Monitoring (PEM). Inman obtained minimal financial backing and persuaded the University of Southampton, UK, to help him start in 1980 what was to become the Drug Safety Research Unit (DSRU). From its start, David Finney was closely associated with the DSRU and became, until 1997, one of its Trustees.

Computers

During 1966-74, David Finney was officially involved in efforts to ensure that every British university had access to a mainframe computer, to meet the demands of scientific research. When he began in drug monitoring, Finney had seen this subject as a form of operational research that would demand imaginative new software for data retrieval and analysis associated with the then rapidly evolving computer technology. It is important to remember that, initially, the CSD had no computer support, but after a few years, it secured some use of a remote computer. However, even in 1980, when his term of service with the Committee on Safety of Medicines (successor to the CSD) was about to end, a civil servant told him firmly that he had no right to ask about progress of a request for a dedicated CSM computer.

Anticipating Signalling

Once a monitoring system has its data systematically stored on a computer, the possibility exists for the computer to output a warning signal as soon as some

measure of association between a drug and a type of event reaches a threshold. Finney did not originate this idea, but in 1974 he reviewed the signalling problem. During his CSD-CSM days there was no formal signalling. He hoped to be able to work on this when CSM secured a computer, but saw it as an interesting future development and regretted leaving the scene before implementation could be seriously discussed.

Looking forward

David Finney was immensely impressed by the enthusiasm and good spirits of the world-wide collaborators who were in Amsterdam. He does have reservations about some new developments, urging an awareness of the unverifiable assumptions in the nature and quality of data, and caution over the use of a mass of clever signalling and interpretative procedures.

He was also forthright in his comments about certain 'advances' in conference presentation. Although he thought both Amsterdam sessions were excellent, he found that some speakers used type fonts that were impossible to read even by someone sitting near the front and with reasonable eyesight. There was also too little light for taking notes, and sometimes when a table or graph was displayed that looked interesting, it disappeared within 30 seconds, before there was time to comprehend it sufficiently to be able to make a comment or ask a question in the following discussion.

David Finney also makes a plea for better and more accurate use of language, particularly in relation to statements about probabilities and percentages; gross faults are common even in scientific journals. In more popular writing, he points out such horrors as that of a recent medical newsletter that stated: 'Migraines affect approximately 14% of women and 7% of men; that's one-fifth of the population'.

His early interests in statistics were primarily in agricultural research; this continued for many years, but he feels that UK governments seem now to have decided that growing food is unimportant. Over the years, he had much to do with biological assay for drug standardisation and like matters. What of the future? He is returning to a problem concerning software for the calibration of thromboplastin. In his spare time, a rare commodity, he enjoys listening to classical music, reading, playing bridge, travel, visiting grandchildren, and seeking to remain sane. Drug safety may have advanced considerably in the last forty years, but all working in the field owe a debt to those who strove in its early years to put effective systems in place. One thing is clear – pharmacovigilance in its international scope would not be what it is today without the central contributions of David Finney in its formative years.

David Finney Papers

A selection of papers by David Finney

Finney D J. (1964) An international drug safeguard plan. *Journal of Chronic Diseases*, 17, 565-581.

Finney D J. (1965) The design and logic of a monitor of drug use. *Journal of Chronic Diseases*, 18, 77-98.

Finney D J. (1974) Systematic signalling of adverse reactions to drugs. *Methods of Information in Medicine*, 13, 1-10.

THE UMC TRAINING COURSE

Participants

Dr John Knight, Dr Alissa Lim,
Miss Nicole McCabe,
Dr Jonica Palmer,
Ms Manja Pertl,
Ms Eliza Rayward,
Dr Jane Worrallo,
Dr Dennis Wright,
(Australia)
Mr Sultan Ahmed, (Bangladesh)
Dr Wenmin Du,
Mr Jing Hua Zhang, (China)
Mr Atendra Prasad, (Fiji)
Ms Sosialine Engko, (Indonesia)
Ms Nancy Ghabboun, (Jordan)
Ms Beatrice Young,
(Macau SAR)
Mrs Zainal Abidin Mazuwin,
(Malaysia)
Ms Nazarita Lanuza,
Ms Marissa Macaraeg,
(Philippines)
Mr Abdullah F.A Al-Mesned,
Mr Khaled J. M. Al-Salman,
(Saudi Arabia)
Ms Pei San Ang,
Ms Bee Him Tan,
(Singapore)
Mr Chulanaga Gnanendra
Sirinath (Chula) Edirisinghe
Arachchige,
(Sri Lanka)
Ms Yaowares Oppamayun,
(Thailand)
Dr Winifred Tumwikirize,
(Uganda)
Ms Thanh Mai Hoang,
Ms Thi Nhung Tran,
(Vietnam)
Mrs Sakhile Velile Dube-Mwedzi,
(Zimbabwe)

Pharmacovigilance training in Australia

Some serious work in the southern hemisphere

Canberra, Australia, is nearly as far from Sweden as you can get, and, in November, about as different as you could imagine from northern Europe. At the invitation of the Australian Therapeutic Goods Administration (TGA), the capital city was the location for a UMC training course in pharmacovigilance, held for the first time away from Uppsala.

Nearly thirty participants from fifteen countries spent two weeks hard at work – on Module 1 (the general principles and practice of pharmacovigilance), and Module 2 (pharmacoepidemiology). Under the leadership of John McEwen, Principal Medical Adviser for the ADR Unit, and his staff, with a galaxy of distinguished visitors, the demands on students were considerable, 8.30 to 5 every day, five days a week.

Many participants came from countries already members of the WHO Programme. They themselves were maybe new in their jobs in pharmacovigilance or were already working but without the background of serious training. Others were from countries with infant ADR monitoring systems, slowly building national awareness and reporting towards the goal of membership of the Programme. Some were more experienced, but looking for additional knowledge and skills, especially in pharmacoepidemiology.

Rural setting

The TGA building is on the outskirts of Canberra, almost surrounded by open country. At lunchtimes, small parties of participants were taken on the 1.4 km walking track which circles the building to view the landscape and to catch glimpses, from time to time, of considerable numbers of wild kangaroos. Warnings about dangerous snakes did not result in sightings, but they are clearly a noticeable feature of local life. After months of drought, everywhere not watered was parched and brown, and farmers and wildlife were suffering badly.

Canberra itself is a remarkable city. Adopted as the



Adventures in the bush

A lunchtime walking group explores the territory around the TGA building – an open landscape with occasional clusters of buildings in the distance. Kangaroo sightings were frequent. Here the trekkers are: Bruce Hugman, Marissa Macaraeg, Eliza Rayward, Beatrice Young, Pei San Ang, Sakhile Dube-Mwedzi, Nancy Ghabboun, Bee Him Tan



capital because the competing demands of Melbourne and Sydney could not be resolved, it is laid out with amazing generosity of open green spaces and tree-planting. Stretching through the very centre of the city is a great lake with a huge fountain. With around 400,000 inhabitants, it covers an enormous area, with suburbs stretching out into the countryside. It boasts a number of important and impressive structures, not least the new parliament building, which is built largely underground into a small hill. (This apparently allows local citizens to walk about and picnic directly above where their representatives are debating national issues.)



Sten Olsson, Erica Walette and John McEwen above the lush central area of Australia's capital city



Winnie Tumwikirize and Ralph Edwards in the sunshine

Ralph flew in to contribute to the course from a trip to South Africa. He is wearing a T-shirt from a South African AIDS awareness campaign: 'I have AIDS' it says on the front; and, on the back: Ambition, Integrity, Determination, Spirit

Expert faculty

The TGA has a fine reputation for its regulatory affairs and its record in ADR monitoring. One of the early members of the WHO Programme, joining in 1968, Australia receives around 10,000 ADR reports annually and is strongly represented in the WHO database.

As well as the TGA team, teaching was provided by Australian Professors Gillian Shenfield, Tony Smith, David Henry and John McNeil. Mary Couper from WHO HQ Geneva, and Ralph Edwards, Sten Olsson, Erica Walette and Bruce Hugman from *the UMC*, also made substantial contributions.

A considerable success

While many participants felt there was insufficient time for the weighty questions under consideration (especially some of those for whom English was not their first language), there was a good deal of lively discussion and the course was greatly appreciated. With representatives from as far apart as Kampala and Hanoi, Riyadh and Shanghai, many new international friendships were made and useful and informative experiences exchanged.

These are some of the comments from the end-of-course evaluation:

- Tremendously helpful! ... not just the training, this offers an excellent opportunity to meet my counterparts from all over the world, who may or may not be in the same situation of progress. We can really learn a lot from each other.
- I found the course very valuable and am grateful that I was able to attend. Not only was the structured part of the course excellent but the interaction with TGA personnel has also been very valuable
- Well organized with good range of topics, including communication
- An excellent 3 days (module II only) - so glad I decided to come. I've learned a lot about a topic which was very much unknown to me and met some amazing people from other countries.
- Thoroughly enjoyable and very applicable.
- Sincere thanks to all those who put so much effort into making this course an outstanding success.
- Thanks for a great course which I think is more than excellent.

Information

The next UMC training course

The next course will be held in 2003, in Uppsala from 12th to 23rd May.

Anyone interested in taking part should contact Sten Olsson at *the UMC* (sten.olsson@who-umc.org).

Participants must find funding themselves for their attendance.



Posed by a sculpture at the front of the main building is the TGA team who provided such great facilities, hospitality and kindness to participants.

Cheng-Long Bai, John McEwen, Ian Boyd, Sharon Woods, Barry Thompson, Richard Hill, Jenny Robinson, Patrick Purcell, and Fay O'Connor.

Introduction

Participants at last November's UMC training course in Canberra speak about their background and their hopes for the future of drug safety in their country. Report and photos: Bruce Hugman.

Snapshots

Du Wenmin

Nancy Gabboun

Tran Thi Nhung & Hoang Thanh Mai



Reactions from Canberra – Challenges ahead

Du Wenmin People's Republic of China

ADR monitoring began in China in 1988. Wenmin, previously a hospital physician, later taking a doctorate in pharmacology, joined the Shanghai centre in 2001. He is Vice-Director in the department of three people (with a physician and a pharmacist) where their responsibilities also include pharmacoepidemiological studies.

He is pleased that they achieved 1,000 ADR reports last year, and hopes soon to double this number. 80% of reports are from hospitals, and about 30% relate to traditional Chinese medicine. He's also involved in the setting up of a record-linkage database study with 500,000 patients in Shanghai, looking at the safety profile of Chinese Medicines. He has recruited 100 community physicians to work in this study.

For him, among the greatest challenges is educating doctors, pharmacists, industry and patients about drug safety and the importance of ADR reporting.

China has a long-established association in drug safety with Australia: Prof Young Ming, one of China's pharmacovigilance pioneers, worked with John McEwen at TGA some years ago; one of the lecturers on this course, Prof Tony Smith from Newcastle University, had just returned from a fortnight in the People's Republic.

Dr Jiang Hua Zhang from the Guangdong Drug Administration was also in Canberra for the course.

Nancy Gabboun Jordan

Nancy is Head of pharmacovigilance in Jordan, with a team of five people working with her. She graduated in pharmacy and did her master's in pharmaceutical technology. Previously she was chief pharmacist in a number of health centres and a community pharmacy inspector.

She is a great drug safety enthusiast and has been working hard to spread the word in Jordan. The ADR centre was set up in 2001 and Jordan became an associate member of the WHO Programme that year. She has a long list of challenges:

- Establishing and approving pharmacovigilance guidelines for Jordan
- Establishing an advisory committee for evaluating ADRs
- Holding lectures for consumers to educate them about drug safety
- Achieving full membership of the WHO Programme

- Establishing pharmacovigilance in a separate centre within the regulatory authority
- Training in evaluating safety information
- Establishing a system for disseminating safety information and regulatory decisions
- Solving software compatibility problems

As in other developing countries, there are many problems to be overcome:

- A relatively immature civil service bureaucracy, with few job descriptions and variable management skills in the health sector
- Widespread irrational use of drugs
- Some accessible drug information but relatively little in Arabic (including patient information which is often in English or French)

Nancy points out that this last issue is important: if there's little printed information and few websites in Arabic, the challenges of informing and educating the population are considerable. 'Pharmacovigilance depends so much on disseminating information,' she says, 'yet there is very little which comes in our own language, except what we are able to provide from the Centre. A lot of extra effort is needed, particularly in rewriting and translation. We're working hard on this through briefings, training and publications.'

Tran Thi Nhung Hoang Thanh Mai Vietnam

Both the participants from Vietnam are medical doctors who work in the national Drug Administration in Hanoi: Hoang Thanh Mai in the regulatory area; Tran Thi Nhung in the ADR monitoring centre. (There is also an ADR centre in Ho Chi Minh City with one further worker.)

Hoang has worked in ADR monitoring since she graduated in 1996, also the year in which Vietnam's ADR monitoring programme was launched. As well as assessing ADR reports she is involved in the management of drug information and drugs and cosmetics advertising.

One of her concerns is that few healthcare professionals seem to understand the importance of pharmacovigilance and that there is much work to be done to turn the tide of opinion. She is keen to find resources for better drug information services, and to develop relationships with international colleagues.

Tran also started her career with ADR monitoring in 1996. She is pleased with their achieving 5000 reports during the time since then, sending 1000 of those to Uppsala, and with running a training course

in pharmacovigilance for doctors and pharmacists. Her greatest challenge is developing the system for managing ADR reports.

Self-medication is very common in Vietnam and many drugs can be bought without prescription, complicating the drug safety picture in the country enormously, and making accurate assessments very difficult.

Winifred Tumwikirize Uganda

Winnie is committed to bringing Uganda into the WHO Programme and was attending the course to prepare herself for the challenge of setting up an ADR monitoring and drug information centre in Mulago Hospital, which is the teaching hospital for the Faculty of Medicine at Makerere University in Kampala.

She is a senior lecturer in the Department of ENT (Ear, Nose and Throat) (and a practising surgeon). She is also a clinical epidemiologist and is now doing her PhD in clinical pharmacology, based in the Department of Pharmacology and Therapeutics at Makerere University.

She says that a high level of irrational drug use in Uganda is a major concern, and that the establishment of pharmacovigilance and the provision good drug information should begin to address the problem.

Chula Edirisinghe Sri Lanka

Chula is a pharmacist in the three-person team at the Drug Regulatory Authority of Sri Lanka. They are responsible for drug registration, GMP inspection and ADR monitoring. Sri Lanka's ADR programme started in 1999 and Chula joined in 2002.

He says his greatest challenge for the next year is to promote ADR monitoring among government officials and healthcare professionals, though he knows that the issues are not given a high priority in a country where war and poverty are having such devastating effects.

Chula has been pleased with the course. Like many others he's found it interesting and demanding, leaving him mentally exhausted at the end of the day and much in need of a refreshing evening beer.

Khaled Al-Salman Abdullah Al-Mesned Saudi Arabia

Khaled and Abdullah are the two pharmacists in the Saudi ADR Centre, based in the General Directorate of Medical Licences and Pharmaceutical Affairs, which is the country's regulatory authority.

Before starting ADR work in 2001, Khaled was a pharmacist in the Prince Saud Hospital, while Abdullah worked in the GMP Unit until a few months ago. As well as work in ADR monitoring, they currently have responsibility for reviewing the registration dossiers, work in the GMP unit, developing the drug information centre and reviewing pharmaceutical company applications relating to leaflet and package changes.

As in many other countries, they feel that their staff and resources are not adequate for the scale of the challenge, and that decisions often take a long time to be taken.

Pharmacovigilance was launched in Saudi Arabia in 1998, and last year there were 15 reports of ADRs and 35 of product quality defects. Both men express the ambition of promoting the Centre and ADR reporting throughout the country and of progress towards membership of the WHO Programme.

Sakhile Velile Dube-Mwedzi Zimbabwe

Before becoming a Senior Regulatory Officer, Sakhile was a hospital pharmacist in Bulawayo, occasionally working as a locum in community pharmacies. She has a B.Pharm (Hons) from the University of Zimbabwe, and is now studying for her MBA at Azaliah Business School.

ADR reports were first received in Zimbabwe in 1985, following publication of the Essential Drugs List in which a reporting form was included. A training initiative in 1996 gave the programme new impetus, but Sakhile says that motivating healthcare personnel to report remains a major problem, though there seems to be some understanding of the importance of pharmacovigilance in the country.

The Zimbabwe ADR Centre is located within the regulatory authority and its work is seen as part and parcel of regulation. There are three officers responsible for this area. They also evaluate applications for registration and inspect premises handling medicines.

One of Sakhile's achievements was piloting a new subsidiary office for the authority, but her greatest challenge for the future is to promote reporting and increase the annual number of reports. Last year there were 72, and to date this year there have been 81.

Winifred Tumwikirize
Chula Edirisinghe
Khaled Al-Salman &
Abdullah Al-Mesned
Sakhile Velile Dube-Mwedzi



Information

Coordinating centre: *Clinical Pharmacology Unit, Verona, Reference Centre for Education and Communication within the WHO Programme for International Drug Monitoring

Veneto Region*: *A. Conforti, R Leone, I Meneghelli, U Moretti, V Piazzetta, GP Velo;*

Lombardia Region: *A Cocci, L Burzilleri, S Scotti, M Venegoni;*

Emilia Romagna Region: *D Motola, N Montanaro*

Quality Control of Data input in a spontaneous reporting database

Signal detection is the main goal in a spontaneous reporting system. The analysis of the reports in a database can be both qualitative and quantitative. Quantitative approaches become increasingly important in relation to the increase in spontaneous reporting rate. However, all the methodologies used, including Proportional Reporting Ratios or Bayesian Method, are based on a correct input of the data in the database. Continuing education of pharmacovigilance staff in data verification and in coding adverse reactions descriptions, drugs and pathologies is important. However some errors can be made; the frequency of these errors and their impact on signal detection analysis are often not evaluated.

A methodology for a quality control of data input in a spontaneous reporting database has been

developed in three regions of northern Italy (Figure 2). We have applied this methodology to our regional database, where trained staff work on data input. A similar analysis has then been made on the new national Italian database on spontaneous reporting, where the data input takes place in more than 400 local health districts and hospitals.¹

Methodology

When evaluating input errors, only spontaneous reporting forms with adequate documentation grade must be selected. We considered only reports where the fields on suspected drugs, reported ADRs, date of onset, start of therapy and dechallenge were filled (documentation grade at least equal to 3). We created a methodology which will be the subject of a future paper on quality control in ADR data, to be submitted for publication. In classifying the errors we looked at their influence on the seriousness of the report, on the drug-reaction causality assessment and on the type of signal. Four possible types of error have been defined:

Type A: input error with no influence on seriousness or causality assessment

Type B: error with influence on the seriousness of a report

Type C: error with influence on causality assessment

Type D: ADR or suspected drug coding error (D+ for serious error with high influence on the type of signal)

The most important fields of the Italian spontaneous reporting form have been evaluated for possible errors (see Figure 1).

Results

Figure 3 shows the characteristics of the regional database compared to the national one. We checked a sample of 350 reports coming from our regional database (preliminarily from Veneto Region), randomly selected among the reports with a date of

Figure 1.

FIELD	POSSIBLE ERRORS
Patient's initials	Type A
Age	The following age categories have been defined: 0-2; 3-14; 15-65; >65 years type A: error with no category change type B: error with category change
Sex	Type A
Source of data	Type A
Date of onset	Type A or type C
Seriousness (hospitalisation, disability, death)	Type B
Outcome	Type B
ADR description (coding)	A) the reaction is present in the terminology exactly as reported by the physician:- <ul style="list-style-type: none"> ■ type A if a different term has been used but the preferred term is the same ■ type D if a different code with a different preferred name has been used (D+ for serious coding errors) B) the reaction is not present in the terminology exactly as reported by the physician:- <ul style="list-style-type: none"> ■ no error if an acceptable preferred term was used ■ type D error if a different preferred term has been used (D+ for serious coding errors)
Suspected Drug (coding)	Type D+ if the suspected drug is changed, type A if only the trade name is changed
Not Suspected Drug (coding)	Type A or type C
Dose (amount, unit and frequency)	Type A
Administration route	Type A
Date of administration	Type A or type C
Indication (ICD code)	Type A or type C
Predisposing condition (ICD code)	Type A or type C
Dechallenge	Type A or type C
Rechallenge	Type A or type C



Figure 2.

	REGIONAL DATABASE	NATIONAL DATABASE
Inhabitants:	18,000,000 (32% of Italian population)	52,000,000
Number of doctors:	28,000 (29% of Italian doctors)	96,000
First year of collection in a database:	1988 (copy of filled reporting form is sent to the regional Authority)	2001
Reporting rate in 2001:	235 reports/million inhabitants (In 2001 about 55% of total Italian reports came from this area)	122 reports/million inhabitants
Centres devoted to data input:	3	Over 400 (117 in the regional area)
Terminologies:	WHO-ART, ICD-9, Italian CODIFA system (for drugs)	WHO-ART, ICD-9, Italian CODIFA system (for drugs)

"The quality of results coming out of a computer cannot be higher than the quality of the records put in"
(DJ Finney, 1965)

Figure 3. Characteristics of the Regional database compared to the National one.



onset ranging from March 2002 to June 2002. Sixty-four reports were excluded from the analysis as they were related to vaccines (with a different reporting form) or had an insufficient documentation grade. Two researchers who usually train the staff in data input checked all reports. About 10% of the reports had an error, more than half of which were Type A errors. Nine reports had a coding error related to use of WHO-ART; three of them were serious. 3.5% of reports were in type C and D categories.

A similar analysis was made on the national database, where the number of pharmacovigilance staff devoted to data entry is much higher and where adequate training is lacking. Again, 350 reports coming from Veneto Region were randomly selected in this database during the same period March 2002 to June 2002. Ninety reports were excluded as vaccines or not documented reports or where no paper form was present to perform the check. About 51% of the reports had an input error, more than half of these errors Type A. Thirty-nine reports had a coding error related to the use of terminologies. Again, by distributing the reports according to the most important error we can see that 18.5% of reports are in type C and D categories. Tables 1 and 2 summarize the results

Table 1. Main results in the databases:

	REGIONAL DATABASE	NATIONAL DATABASE
Number of selected reports	350	350
Number of included reports	286	260
Number of reports with at least one error	31	134
% of reports with at least one error	10.8%	51.5%
Total number of errors	35	191

Conclusions

Errors are always possible in data input, even if some of them can be avoided with a good input program. However input errors are not the same. Most of them

Table 2. Distribution of the reports in the regional and national databases according to the most serious errors (A<B<C<D<D+):

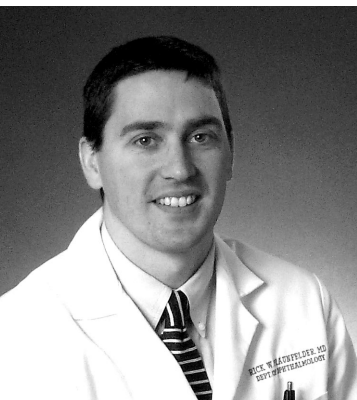
Type of error	REGIONAL DATABASE		NATIONAL DATABASE	
	Number	%	Number	%
No error	255	89.2	126	48.5
A	17	5.9	75	28.8
B	4	1.4	11	4.2
C	1	0.4	9	3.5
D	6	2.1	24	9.2
D+	3	1.0	15	5.8
Total	286	100	260	100

have practically no consequences on signal detection (type A errors); others may influence the computerized quantitative analysis. A critical point in this respect is correct use of terminologies, particularly in relation to ADRs reactions since physicians often use terms that have to be coded. The comparison between the two Italian databases shows the importance of training of pharmacovigilance staff in data entry and coding, perhaps suggesting that data input should be centralized to a regional or national level. Furthermore, periodic analysis of a randomly-selected sample could give an estimate of the quality of the work done by the staff. There are two questions raised by this analysis: how frequent are these errors in spontaneous reporting databases and what is the influence/impact of these errors in signal detection?

Footnote

¹ Local authorities in Italy send their reports directly to the National Centre at the National Ministry of Health, not via a Regional Centre – the 'ADR Reporting in Italy' section in UR20 did not make this clear.

Dr Fraunfelder, father and son: Frederick T (top), and Frederick W (below)



Important ADR website

The National Registry of Drug Induced Ocular Side Effects was founded in 1976 in Little Rock, Arkansas by Dr Frederick (Fritz) T Fraunfelder. The goal was to create an international clearinghouse of drug information on adverse ocular events associated with drugs and biologics. The underlying principle of the Registry is to generate early signals of adverse ocular reactions secondary to medications based on suspicions of practising clinicians.

Reporting

In addition to collecting spontaneous reports from clinicians, the Registry accumulates data from the World Health Organization's Uppsala Monitoring Centre, the JSA Food and Drug Administration, pharmaceutical companies, and periodic screening of the world's literature.

The National Registry of Drug Induced Ocular Side Effects is now online at www.eyedrugregistry.com and includes some important ADRs occurring in ophthalmology.

Database

The Registry maintains an extensive database specific only to ocular reactions caused by systemic or ocular medication. Dr Fraunfelder's son Dr Frederick (Rick) W Fraunfelder, is the current Director of the Registry with the same mission: to provide

practising clinicians with data on adverse ocular side effects which are not available anywhere else in the world. Reports are classified according to the WHO causality assessment guide.

Membership Information

The Registry will be offering memberships that allow physicians around the world to search its database. This facility will be available shortly.

Recent investigations in brief:

Bisphosphonates such as Pamidronate disodium (Aredia®), Alendronic acid (Fosamax®), other bisphosphonates (ibandronate, risedronate, zoledronate), used to inhibit bone resorption in managing hypocalcaemia of various cancers, and for osteoporosis of menopausal women. The visual side effects identified have included scleritis, episcleritis, anterior uveitis and non-specific conjunctivitis. It is important to note that this is the first class of medicine ever to have been reported to cause scleritis; medication must be stopped before the scleritis will resolve.

Topiramate (Topamax®) used to treat seizure, migraine, bipolar disorder, depression, neuropathic pain. Off label use as weight loss medication. The visual side effects (from 114 cases reported to National Registry) include acute secondary angle-closure glaucoma, myopia up to 8 diopters, and suprachoroidal effusion.

Voriconazole (Vfend®), a new anti-fungal FDA approved in May 2002, has shown several visual side effects including altered visual perception (38%), colour vision abnormalities, photophobia and depressed visual fields.

Contacts

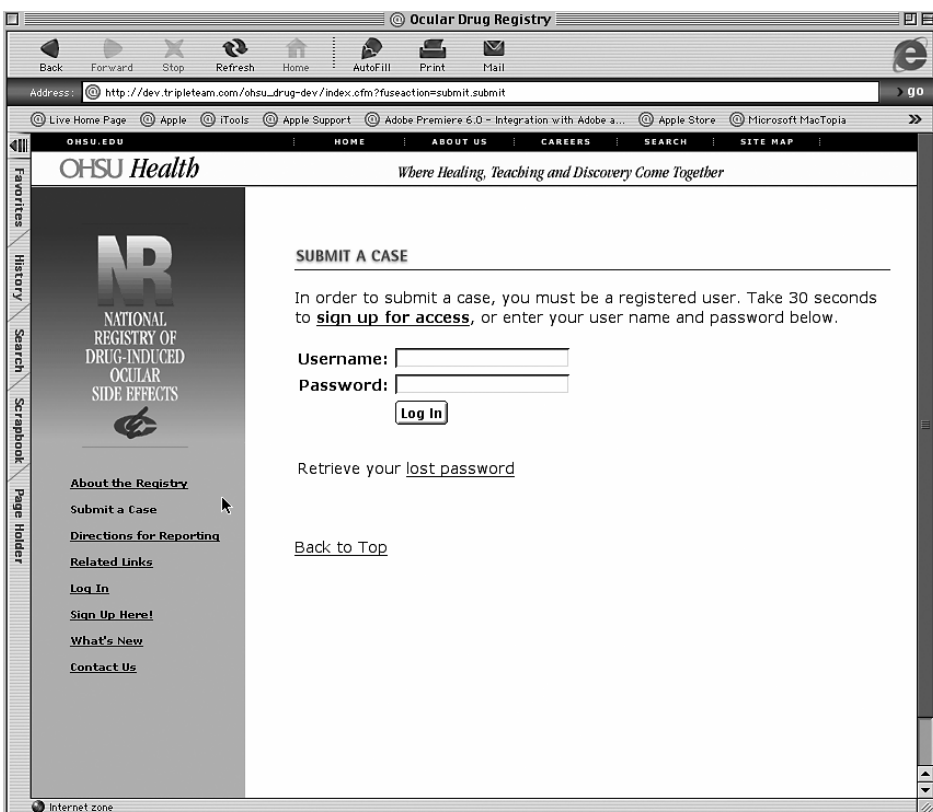
All case reports, as well as any impressions, even without specific cases, are welcome and can be submitted online by registered users (registration to the website is free).

To contact the Registry,

Tel: +1(503) 494-5686, or
Fax: +1(503) 494-4286.

Case Reports may also be faxed, or mailed to:

National Registry of Drug-Induced Ocular Side Effects
3375 SW Terwilliger Blvd.
Portland,
OR 97201,
USA



ATC working group in Morocco

From 21-22 October 2002 there was a training workshop in Casablanca for the application of Anatomical Therapeutic Chemical classification (ATC) and Defined Daily Doses (DDD) Methodology in drug utilization research, arranged by WHO in Geneva. The participants for this workshop came from Egypt, Iran, Italy, Jordan, Morocco, Saudi Arabia, Syria, Tunisia and USA. Speakers at the workshops were the members and observers of the ATC/DDD working group.

Monica Pettersson from *the UMC* talked about how the ATC and DDD systems are used within the WHO Programme for International Drug Monitoring. The ATC classification is a part of the WHO Drug Dictionary (WHO DD). All drug names in the dictionary have one or more ATC codes assigned. All drug names in all case reports in the WHO adverse reactions database are therefore linked to an ATC code. This facilitates searches in the WHO adverse reaction database. For instance if someone is interested in all statins (HMG CoA reductase inhibitors), they do not have to find all the different drug names in that group. The selection is based on the ATC code, (C10AA) and that will retrieve all statins that have been entered in the WHO DD, and the case reports with these drugs reported will be found in the database.

The DDDs are used together with sales data, which is available from IMS in London, to calculate the number of defined daily doses that have been sold. This is sometimes used in analysis of adverse reactions and forms part of the ADRespherics service, Nimbus.

In connection with the training workshop, the working group of the ATC and DDD classification held a meeting, on the 23-24 of October, also in Casablanca. The host for both the workshop and the working group meeting was Professor Mohammed Hassar, who provided fine hospitality for all.

Monica Pettersson also made a visit to the Moroccan National Pharmacovigilance Centre in Rabat. "Dr Amina Tebaa was my host, and she showed me around their offices. They are not only running a pharmacovigilance programme, but also dealing with teratovigilance, pharmacodependence, vaccinovigilance, phytovigilance and hemovigilance. The centre has a telephone service open 24 hours a day, to answer questions from health professionals as well as the public. Of around 5,000 cases stored, 1,100 of them are adverse reaction reports, which have been submitted to the WHO database. They had just started to move into new premises."

Pictured

Some members of the ATC working group



Morocco will be the venue for the 2003 Annual Meeting of the International Society of Pharmacovigilance (see course and conference list p18).

Expecting the Worst

At the 23rd Annual Meeting of representatives of National Centres in Tunis, November 2000, a session was devoted to crisis management. The deliberations during that session resulted in a request to *the UMC* to develop a summary on the theory and practice of good crisis management, with guidelines tailored to the needs of pharmacovigilance centres. *the UMC* commissioned Bruce Hugman to research the area and prepare a draft text. This was presented to the Annual Meeting in Dunedin 2001. After having taken account of comments and ideas offered by the early readers of the document and adding some topical case studies, the first edition of the guidelines are now being printed. The crisis management guidelines will be made available free of charge for National Pharmacovigilance Centres in January 2003.

COURSES & CONFERENCES

DATES	TITLE	PLACE	ORGANISER/CONTACT
27-28 January 2003	Drug-Induced Hepatotoxicity	Washington USA	Tel: +1 800-686-2276 www.pharmedassociates.com
29-31 January 2003	Medical Aspects of Adverse Drug Reactions	Southampton UK	Jan Phillips, Drug Safety Research Unit Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org www.dsru.org
13-14 February 2003	Risk Management in Pharmacovigilance	London UK	Management Forum Ltd Tel: +44 (0) 1483 570099 Fax: +44 (0) 1483 536424 E-mail: info@management-forum.co.uk
18 February – 30 June	Certificate in Pharmacoepidemiology and Pharmacovigilance (London School of Hygiene and Tropical Medicine)	London UK	Course Organizer Tel: +44 (0)20 7927 2489 Fax: +44 (0)20 7637 3238 E-mail: deborah.curle@lshtm.ac.uk www.lshtm.ac.uk
19 February 2003	Adverse Event Reporting and Pharmacovigilance	London UK	Rostrum Tel: +44 (0)118 933 5343 E-mail: rostrum@mdsps.com www.rostrumtraining.com
5-7 March 2003	e-ternal medical progress? 15th Annual DIA Euro Meeting (Pharmacovigilance and epidemiology track)	Rome Italy	DIA Office, Basel Tel: +41 61 386 9393 Fax: +41 61 386 9390 E-mail: diaeurope@diaeurope.org
24-25 March	15th Annual Conference on Pharmacovigilance: ADR Monitoring and Safety Surveillance Strategies in Europe and the USA	London UK	Management Forum Ltd Tel: +44 (0) 1483 570099 Fax: +44 (0) 1483 536424 E-mail: info@management-forum.co.uk
4-5 April 2003	IV Jornadas de Farmacovigilancia	Valencia Spain	Ms Pilar Lorenzo, Viajes El Corte Inglés Tel: +34 91 2042600 www.msc.es/agemed/
14 April 2003	Drug Treatment: Maximising Benefit and Minimising Risk	Edinburgh Scotland	Royal College of Physicians of Edinburgh in association with ISPE and ISPOR Tel: +44(0)131 225 7324 Fax: +44(0)131 220 4393 E-mail: e.strawn@rcpe.ac.uk
14-16 April 2003	24th Journées de Pharmacovigilance (Société Française de Pharmacologie)	Lille France	Département de Pharmacologie: Tel: +33 (0)3 20 44 54 49 Fax: +33 (0)3 20 62 69 92 E-mail: clibersa@chru-lille.fr
12-23 May 2003	Pharmacovigilance – the Study of Adverse Drug Reactions	Uppsala Sweden	Sten Olsson, the Uppsala Monitoring Centre, Stora Torget 3, S-753 20 Uppsala, Sweden E-mail: sten.olsson@who-umc.org
14 - 15 May 2003	How to Read a Paper – A Course on Critical Appraisal	Southampton UK	Jan Phillips, Drug Safety Research Unit Tel: +44 (0)23 8040 8621 E-mail: jan.phillips@dsru.org www.dsru.org
23 June 2003	Adverse Event Reporting and Pharmacovigilance	London UK	Rostrum Tel: +44 (0)118 933 5343 E-mail: rostrum@mdsps.com www.rostrumtraining.com
24-28 June 2003	6th Congress of EACPT. <i>There is a 'pharmacovigilance and communication' workshop.</i>	Istanbul Turkey	Flap Tour Tel: +90-312 442 07 00 Fax: +90 312 440 77 99 E-mail: flaptour@6theacpt.org
21-24 August 2003	19th ISPE Conference and the 1st International Conference on Therapeutic Risk Management	Philadelphia USA	Tel: +1 301 718 6500 Fax: +1 301 656 0989 E-mail: ispe@paimgmt.com www.pharmacoepi.org/meetings/index.html
9-11 October 2003	ISoP Annual Meeting (preceded by training courses)	Marrakech Morocco	Conference secretariat Fax: +212 37 75 60 87 www.isop2003.org

WHO Drug Dictionary

Updates – 3rd Quarter 2002

The new versions of the computerised WHO Drug Dictionary (WHO-DD) and WHO Adverse Reaction Dictionary (WHO-ART), containing information for the 3rd quarter of 2002 are now available. These were sent to subscribers during December 2002. The WHO-DD pack contained the updated version of WHO-DD. We are sorry for the delay this last quarter, but hope you feel it has been worth the wait! We have recently completed a major development of the WHO Drug Dictionary.

Getting familiar with the new DD format

As well as the new C format, the CD also contains two versions of the previous B format and all the documentation needed to make full use of the Drug Dictionary. Among the changes, we have introduced extra fields to provide important new information (including herbal products) to DD users.

Need help?

If you have any queries about the content of the update pack, or any detail of the DD itself, or need further information about your current subscription or how to upgrade it, do call *the* UMC.

You can e-mail: drugdictionary@who-umc.org for comments about the DD, corrections, additions, and inger.forsell@who-umc.org for queries about your subscription.

If you are a subscriber to either WHO DD or WHO-ART and have not yet received the update, please contact Inger Forsell (inger.forsell@who-umc.org).

Data files for the 4th quarter of 2002 should be available during February 2003.

Conference exhibitions

UMC staff are planning to attend the following conferences in 2003:

- DIA EuroMeeting – Rome, March 5-7
- DIA Annual Clinical Data Management conference – Philadelphia, March 31 – April 2
- DIA Annual Meeting – San Antonio, TX, June 15-19
- ISPE – Philadelphia, August 21-24

We look forward to seeing many of you at these events; if you wish to arrange a meeting with us at one of them, please contact Mats Persson.

Have you moved ?

If there is a mistake in our database, or you have changed your address, do please let us know. Either post or fax the envelope label to us, with corrections marked on it, or simply e-mail your correct address to us. We will then be able to correct our address lists. Thank you!

The Centre recently welcomed **Elizabeth Bengtsson** to work alongside Mats Persson and Inger Forsell in the Sales and Marketing Department.

Elizabeth has considerable experience in the field of pharmaceuticals marketing. She worked at Amersham Biosciences as assistant with the global Marketing department – Chromatography Media & Systems (the products used in downstream processes in pharmaceutical production around the world). In addition to supporting the marketing department, she had responsibility for product registrations and updates in the administrative systems for the Engineering department and handling the product

data base, including updates, new registrations etc. Elizabeth's father is Russian and her mother from France, but they met in Uruguay where she was born, and she ended up in Sweden when she was 9. She met her husband Anders when she was 14 and, twenty happy years later, has 3 children: Emelie 16, Isabell 14 and Viktor 7.

As well as fishing, summer and winter – she catches turbot – now and then she dances tango. "My father is a tango instructor in his spare time (normally he is a bus driver)."

A truly international addition to *the* UMC team!

Staff News





Ralph Edwards
Professor in Medicine, Director

Sten Olsson
Head of External Affairs

Cecilia Biriell
Head of Internal Affairs

Marie Lindquist
Head of Data Management & Research, General Manager

Mats Persson
Head of Marketing & Sales, Business Development Manager

Marjatta Leván
Manager, Finance and Personnel

Mohamed Farah
Programme Leader, Traditional Medicines

Malin Ståhl
Programme Leader, Signal Detection

Andrew Bate
Programme Leader, Signal Research Methodology

Helena Fucik
Data Processing Co-ordinator

Monica Pettersson
Programme Leader, Signal Analysis

Malin Nord
Programme leader, Database Products

William Frempong
Data Management

Annica Lundström
Data Management

Erica Walette
Programme Leader, Database Services

Anna-Karin Flygare
Medical Terminologies

Jenny Ericsson
Data Management

Jessica Nilsson
Data Management

Anne Kiuru
Signal Detection & Analysis

Helena Sjöström
Data Management

Daniel von Sydow
Project Co-ordinator

Sven Purbe
Data Management & Quality Assurance Co-ordinator

Anna Lindquist
Team Support, Web Editor

Inger Forsell
Sales & Customer Relations Executive

Elizabeth Bengtsson
Sales and Marketing

Anneli Lennartsson
Team Support, Internal Affairs

Sally Eriksson
Team Support

Geoffrey Bowring
External Affairs Co-ordinator

Magnus Larsson
Programme Leader, IT Systems Development

Bo Östling
Senior Systems Developer

Stefan Lewenfolk
Systems Developer

New member of UMC Review Panel: Alfonso Carvajal

Dr Carvajal was born in El Toboso, studied Medicine at the University of Madrid and obtained his PhD at the University of Valladolid where he currently teaches pharmacology in the Faculty of Medicine. He has been involved in experimental research from 1978 to 1987. He has also worked at the Department of Pharmacology of King's College, London, the Laboratoire de Pharmacologie at the School of Medicine in Toulouse, and in the Department of Pharmacology of the Royal College of Surgeons in Dublin.

Since 1987, Dr Carvajal has been involved in pharmacoepidemiological research. He runs a Regional Centre of Pharmacovigilance in Valladolid and actively collaborates with the Spanish Medicines Agency; he has translated the Medical Dictionary for Regulatory Activities (MedDRA) into Spanish. Currently, he is head of the Institute of Pharmacoepidemiology devoted to the investigation of the safety of medicines. He is a co-author of the Meyler's Side Effects of Drugs series. He undertook pharmacoepidemiological research at Caro Research in Concord (Massachusetts).



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