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Uppsala reports

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

MESSAGE FROM THE DIRECTOR

If it's true that one of the only constants in modern life is change, it's equally evident to us all that change is taking place at an ever-accelerating pace.

An important issue for us is the commercial pressure influencing the speed at which pharmaceutical companies need to bring new drugs to market. Their search for 'blockbuster' drugs which can be marketed globally and deliver significant profits also raises concerns for pharmacovigilance.

The shortened timescales for drug development and the increasing outsourcing of functions make for an environment where some pre-marketing safety issues may go unnoticed.

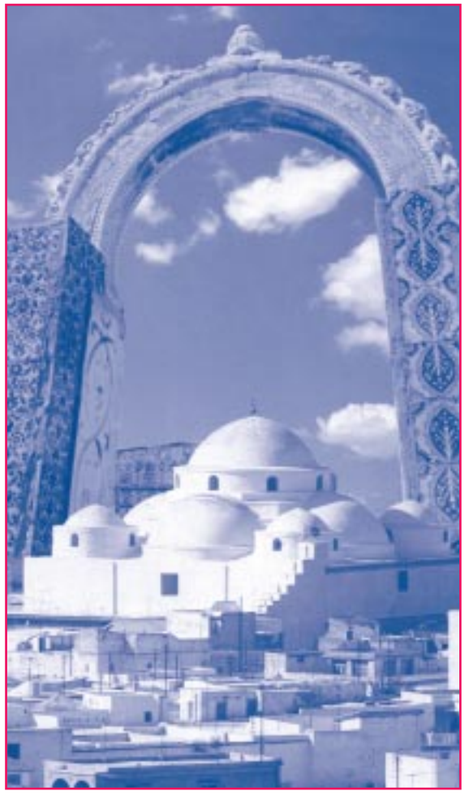
The high challenges for the global pharmacovigilance community are to develop ever more effective methods of finding early signals of drug problems and rapidly to determine true benefits and risks. If the scientific challenges are great, then so are those of communication: more knowledge being developed at an accelerating pace needs more and more refined and transparent methods and channels of communication. Our goal of universal rational drug use will not be achieved easily!

These - and many other issues - are the constant theme of the work of *the* UMC and they will be among the many topics which we shall be examining at the Annual Meeting of Member Countries in Tunisia in November. I hope we shall see many of you there to join in the global effort to stay abreast - and ahead - of so much demanding change.

Ralph Edwards

23rd Annual Meeting **of WHO Drug Monitoring Programme**

The Tunisian Ministry of Health has kindly extended an invitation to WHO to organize the 23rd Annual Meeting of Representatives of National Centres participating in the WHO International Drug Monitoring Programme. This will be held in Tunis on 12-14 of November, 2000, with a pre-meeting tutorial on 11 November.



The meeting will be held immediately following the 7th Mediterranean Congress of Clinical Pharmacology, Carthagia, Tunisia, 8-10 November 2000.

The objectives of the **Annual Meeting** are:

- **to provide a forum for countries participating in the programme to meet and discuss issues of current concern**
- **for latest developments, best practice and methodology in pharmacovigilance to be explained, promoted and discussed**
- **for *the* UMC to exercise its accountability to member countries and seek their advice as to future directions, service levels and research priorities**
- **to provide a supportive, informative, sociable event in the pursuit of more effective pharmacovigilance worldwide and in developing productive relationships between member countries and other key players.**

National Centres have been invited to suggest topics for the meeting agenda. Newcomer countries to the WHO programme will be invited to present their pharmacovigilance systems as posters. These will be published in *Uppsala Reports* following the meeting.

the UMC will work closely with the Tunisian hosts to arrange all practical matters relating to the **National Centres Meeting.** If you have any questions or suggestions please contact Sten Olsson at *the* UMC.

Questions regarding the **Clinical Pharmacology Congress** may be submitted to **Professor Belkahia**, Centre National de Pharmacovigilance Sis Hôpital Charles Nicolle, TUNIS 1006, Tunisia **Tel: +216-1-562 098 Fax: +216-1-571 390 E-mail:chalbi.belkahia@rns.tn**

News *from the* Uppsala Monitoring Centre

Sten in a playful mood on his 21st birthday (now that's a lot of hot air!)

Changes to The WHO Adverse Reaction Newsletter

Since 1981, *the* UMC has produced and distributed (to participating National Centres on a three-monthly basis) *the WHO Adverse Reactions Newsletter*. The focus of the newsletter has been information on specific drug related safety issues. The content has been based on communications, including national ADR bulletins, provided by the participating countries, supplemented with information from the WHO database.

WHO Headquarters, Geneva, later started an information sharing activity, including distribution of the *WHO Pharmaceuticals Newsletter*, which is sent to specially designated drug information officers in all member countries of WHO and a great number of other experts and partners around the world. A substantial part of the *WHO Pharmaceuticals Newsletter* deals with information on adverse reactions and safety aspects of individual medicinal products. Although there is a substantial overlap in content between these two publications, the distribution is somewhat different.

At a meeting in Geneva in February 2000, it was agreed that, to avoid duplication of work, *the* UMC would stop producing the *WHO Adverse Reactions Newsletter*, but instead carry the full responsibility for the adverse reaction section of the *WHO Pharmaceuticals Newsletter.*

By ensuring that all National Centres are included on the mailing list of the *WHO Pharmaceuticals Newsletter* all recipients should now get a much improved drug information service!

More Internet Based Seminars & Training Courses

In August 1999, we made our first three lectures, including sound recordings and visual material, available on *the* UMC web-site (www.who-umc.org/presentations). We were curious to know if our clients would appreciate this new technology for distribution of information and knowledge.

Unfortunately we've had very little feed-back to this initiative so far, either positive or negative. We imagine that we would have received negative comments if our target audience had experienced technical difficulties in accessing the seminars, so we've decided to keep on adding new presentations on to our website.

The latest entry is a recording from the tutorial session of the National Centres meeting in Ankara, September 1999. The title is **Historical Development of the WHO Drug Monitoring Programme**, presented by Sten Olsson, of *the* UMC.

To listen to the presentations and watch the visual material you need to have:

- *access to a computer with soundcard and speakers*
- *an Internet connection and an Internet web browser equivalent to Netscape or Explorer Version 3 or higher*
- *the system must also enable the receipt of Java Aplets.*

Responding to an increasing demand for training about the structure and proper use of *the* UMC products *WHO Drug Dictionary* and *WHO Adverse Reaction Terminology*, we have recently developed Internet-based training courses, including presentations of facts, student tests and facilities for e-mail discussions with a tutor.

If you are interested in taking any of these courses, please contact Liza Storm **(liza.storm@who-umc.org)**.

PLEASE LET US KNOW!

To guide us in deciding whether Internet-based training and information sharing is a technology for the future we need your views, comments and experiences. All types of comments, positive or negative, technical or content related are most welcome. Please send your message to Sten Olsson (sten.olsson@who-umc.org).

the UMC negotiating literature coverage with ADIS Press

Discussions between *the* UMC and ADIS International Ltd, publishers of the review journal *Reactions Weekly*, have resulted in National Centres participating in the WHO International Drug Monitoring Programme getting an offer from ADIS to subscribe to *Reactions Weekly* at a substantially reduced rate.

If the offer is accepted by National Centres, *the* UMC will assist *Reactions Weekly* in gaining up-to-date access to published material from national pharmacovigilance centres. This information will be reviewed by ADIS and included in the weekly journal. Accordingly, National Centres are offered a quicker distribution of material from National Centres and coverage of everything written about adverse drug reactions in approximately 1,800 journals/ newsletters from around the world!

National Pharmacovigilance Systems (NPS) 3rd Edition

Included with Uppsala Reports 11 was a flyer announcing the availability of the 2nd edition of our publication ***National Pharmacovigilance Systems***, describing the pharmacovigilance set-up in 57 countries. The response was very positive and we had a lot of requests for the publication.

PLEASE HELP US PLAN THE 3RD EDITION!

We are now starting the planning phase for the 3rd edition of NPS, scheduled to be published in 2001. We are considering how to amend the contents to make the publication more informative and up-to-date. We are also thinking about other ways of distributing the information (e.g. on CD-ROM or on Internet). If you have suggestions regarding the content or the format of this valuable reference source *(and your suggestions are most welcome!)*, please contact Sten Olsson at *the* UMC.

Collaboration with University of Cape Town on Traditional Medicines

On 8 February 2000, **Professor Peter Folb**, Department of Pharmacology, University of Cape Town (UCT), South Africa visited *the* UMC to discuss collaboration between the UCT and *the* UMC in the area of traditional medicines. It was agreed that the two parties

(Continue overleaf)

will share information in their respective databases with the aim of making the supporting structures compatible. The components that will be shared initially are: the ATC herbal register; *the* UMC herbal substances register and the botanical, therapeutic, chemistry and pharmacology information available to UCT.

The aim is to expand this into a Pan-African initiative in the course of time and to see if other countries in the WHO drug monitoring programme might like to join in due course. An important component of the collaboration will be student exchange and training with the view of building capacity in this field.

Governmental Review

As mentioned in Uppsala Reports 10 and 11, the WHO Collaborating Centre for International Drug Monitoring *(the Uppsala Monitoring Centre)* was subjected to an official review in 1999, commissioned by the Swedish Government. The review team presented its report to the Government in September 1999. This report, 90 pages (Swedish Governmental Official Report SOU 1999:99) is now available in English and may be obtained from *the* UMC.

Discussion on the National and International Management of Adverse Events following Immunization (AEFI)

In early February 2000, *the* UMC hosted a discussion about vaccine safety with participants from WHO Headquarters and University of Cape Town, South Africa. WHO was represented by Philippe Duclos and Julie Milstein (Vaccine and Biologicals) and Mary Couper (Essential Drugs and Medicines Policy). Ushma Mehta and Prof Peter Folb represented the University of Cape Town. Ralph Edwards and Ronald Meyboom attended on behalf of *the* UMC.

Among other things it was agreed that:

- in general, the principles of causality assessment are the same as those adopted in general clinical decision-making. Therefore, vaccine and non-vaccine signals do not differ significantly although the public response might be quantitatively different. Vaccine safety monitoring has the added dimension of not only protecting the patient but also the immunization programme. In the case of vaccines there is a more urgent need to investigate something which might impact on patient safety or the immunization programme
- there is a need to cross-fertilise the fields of vaccine safety and pharmacovigilance. Closer collaboration should be established between the vaccine and biologicals department at WHO and *the* UMC
- the Cape Town group will develop a training manual which will provide regulatory authorities with the information and skills necessary to deal with vaccine safety issues
- *the* UMC training programme (which is run every alternate year) will include a session on the special monitoring issues relating to vaccines
- *the* UMC would promote the idea among National Centres that for serious, unexpected ADRs, a field evaluation would need to be done before a probable causal association is entered into the database
- The Annual Meeting of National Centres would include a session on vaccines
- the use of data-mining tools to identify signals in *the* UMC database could be useful in specific relation to vaccine signals.

(Ushma Mehta)

Signal Review Panel - WE'VE GOT SOME NEW REVIEWERS!

As a result of our request in Uppsala Reports 10 and 11 for volunteers to help us review the output from the WHO database in the search for new adverse reaction signals, we are now happy to let you know that additional experts have joined our team of signal reviewers.

They are:

Dr Emilio Sanz, Department of Pharmacology, University of Laguna, Tenerife, Spain.
E-mail: esanz@ull.es.
He will focus on cardiac reactions and neonatal and infancy disorders.

Dr Mabel Burger, Department of Toxicology, Hospital De Clínicas, Montevideo, Uruguay.
E-mail: hcciat@hc.edu.uy.
She will deal with poison specific reactions.

Dr David Mansoor, Ministry of Health, Wellington, New Zealand.
E-mail: ossi_mansoor@moh.govt.nz.
He will be particularly concerned with vaccine related reactions.

Dr Elliot Brown, Barnet, Herts, United Kingdom. *The focus of his work has still not been decided.*

Dr P O Lundberg, Department of Neurology, Academic Hospital, Uppsala.
He will be scrutinizing potential signals relating to reproductive disorders.

We are negotiating the terms of collaboration with additional clinical experts who are willing to assist us in this important task. We intend to present the complete review panel on our website very soon.

The first meeting of the review panel for signal analysis was held in Uppsala, 23-24 August, 1999. The second meeting will take place on 13-15 September, 2000, also in Uppsala.

Organizational changes at *the* UMC

As of January 2000, we have modified our internal organization to improve our operational efficiency. Our aim is to have a performance oriented, flexible organization with clear responsibilities, but without a rigid hierarchical structure. In addition to our main areas - External Affairs, Public Sector Clients; External Affairs, Commercial Clients; Data Management & Research; Information Technology Systems and Internal Affairs - we have a number of identified programmes. For each of these, we have a programme leader who is responsible for the ongoing activities within the programme.

We hope that the new organizational structure will help us achieve our goals of a first class and scientifically sound contribution to worldwide medicines safety, and an excellent and timely service to all our clients.

Staff changes

From April 2000, Malin Nord will be on maternity leave from *the* UMC for a while. Fortunately we have managed to find a competent replacement in **Anne Kiuru**. Anne has a MSc in pharmaceutical biosciences from the University of Uppsala, has studied at the Uppsala Graduate School in biomedical research and has experience within several fields of pharmaceutical and biomedical research. She will be handling incoming reports from National Centres, corresponding with National Centres about their reporting to *the* UMC and updating the WHO Drug Dictionary with new drugs on request from member countries and external inquirers. Anne speaks Swedish, English and Finnish. Her e-mail address is:
anne.kiuru@who-umc.org

the UMC'S VISITORS BOOK!

(Dr Daniela Stanciu)

Dr Daniela Stanciu, Head of the National Centre in **Romania**, visited *the* UMC on 7-18 February, 2000, as part of a European Union development plan for the pharmacovigilance system in Romania. During her stay she studied in detail the processing of adverse reaction reports from around the world and the production of information and signals from the various data sources available at *the* UMC. The focus of the programme was on how a National Centre may benefit from being part of a global network of National Centres and what is required from each member of this network. Dr Stanciu also paid a visit to the Swedish pharmacovigilance centre at the Medical Products Agency.

As part of the next phase in the development plan for the Romanian pharmacovigilance system, two promotional seminars for key health professionals were held in Bucharest from 3-4 April and in the University City of Cluj from 6-7 April, 2000. Sten Olsson from *the* UMC was one of the lecturers at these seminars.

TAIWANESE DELEGATION

A delegation representing different partners of the Taiwanese pharmaceutical sector visited *the* UMC on 25 February, 2000. Head of the delegation was **Professor Oliver Yoa-pu Hu**, Director General of the Bureau of Pharmaceutical Affairs, Department of Health. A great interest in the activities and services of the WHO drug monitoring programme was expressed by members of the delegation. The possibility of a technical collaboration between *the* UMC and the Taiwanese authorities was discussed in light of the fact that Taiwan is not a member of WHO.

(Anne Kiuru)

Promoting Adverse Reaction reporting!

In 1997, we distributed a folder to National Centres with ***examples of educational and promotional material*** used in various countries to stimulate reporting of adverse drug reactions. The thought was to share ideas and designs within our network and thus facilitate the adaptation of existing material into, for example, other language versions. Our mission is (on a global scale) to utilize educational and promotional material as efficiently as possible, avoiding unnecessary duplication of work.

We now want to update our collection of material and proceed to another level. With the increasing use of the Internet it has become common practice to download material from an Internet website for local use, manipulation or printing. It's our ambition at *the* UMC to develop our website into a repository for educational and promotional aids in pharmacovigilance. We would like it to be used by anyone who is interested in this area.

PLEASE HELP !

To accomplish this we need your help! We kindly ask everyone involved in trying to stimulate adverse reaction reporting to send us one copy of every piece of material produced and currently in use. Here are some examples of materials currently used:

- **printed material (posters, stickers, calenders etc)**
- **reporting manuals or guidelines**
- **educational slide shows e.g. in MS PowerPoint or other format**
- **educational video or audio tape**
- **other materials like; pens, rulers, magnets, mousemats, coasters etc.**

Please e-mail us digital versions of your materials, or post actual items to Sten Olsson at the UMC. We're most interested in materials produced in the local language and not only English versions.

The origin of the material received as well as any specific authorship will of course be clearly stated as we make it available to others. If you prefer not to have your computerized material made available directly from *the* UMC website, but kept on your own Internet server, we can set up a direct link.

Results of educational or promotional interventions

When educating newcomers to the field of pharmacovigilance on how to encourage reporting, we refer to the variety of activities that have been undertaken in our member countries. It is, however, difficult to find documentation on the effects of the different educational or promotional interventions. We are not sure which methods are effective and which are not, or why.

To remedy this situation we would like to collect information about any documented results of interventions that have been carried out to stimulate ADR reporting. We are interested in published reports as well as internal documents. The intention is to make the results widely known through ***Uppsala Reports*** and to use them in our training activities. If you have documented results of your own activities in this area or know of other studies, please do let us know. ❑

COURSES & MEETINGS in PHARMACOVIGILANCE

- IIR is arranging the **East Coast Annual Adverse Drug Reaction Reporting Conference** in Bethesda, Maryland, USA, 22-24 May, 2000.
  For **information** contact IIR at:
  Tel: +1-888-670 8200
  Fax: +1-941-365 2507

- Vision in Business Ltd is organizing a conference on **QT Prolongation and Safety Pharmacology** in Paris, France, 20-21 June, 2000.
  For more **information** contact Vision in Business at:
  Tel: +44-20-7256 5188
  Fax: +44-20-7256 5768
  E-mail: postmaster@visibis3.demon.co.uk

- The European Society of Pharmacovigilance (ESOP) is organizing a **one-day training course** on individual case management in Bordeaux, 26 June, 2000. The course is aimed at entry to mid-level staff in the industry and from centres dealing with cases on a daily basis. For more **information** contact:
  Véronique Gigou: ARME-Pharmacovigilance,
  Hôpital Pellegrin, 33076 Bordeaux Cedex.
  Fax: +33 556 98 12 91
  E-mail:arme-p@pharmacologie.u-bordeaux2.fr

- IBC Global Conferences presents the **7th International Annual Conference on Adverse Drug Reactions** in London, UK, 29-30 June, 2000.
  For more **information** contact Penny Richards at IBC:
  Tel: +44-20-7453 5496
  Fax: +44-20-7631 3214

- IPT (International Pharmaceutical Training) is organizing two 2½ day training courses in London, UK. The dates are 10-12 July and 18-20 September, 2000. The title of the course is **Introduction to Adverse Event Reporting & Pharmacovigilance**. Course leader is Dr Curt Appel, of Kusuri Canada Corp, (one of *the* UMC signal reviewers).
  For more **information** contact IPT at:
  Tel: +44-20-7915 5055
  Fax: +44-20-7915 5056
  E-mail: registration@iir-conferences.com

- The Swedish foundation KILEN - Consumer Institute for Medicines and Health - is organizing an international conference in Sigtuna, just outside Stockholm, Sweden, 29 September - 1 October 2000 entitled: **Consumer Reports on Medicines**. The introductory speech will be made by Ralph Edwards, *the* UMC.

  This will be a working conference. Participants are asked to respond to five questions before arrival:

1. Presentation (yourself and the organisation you represent)
2. If there is a system of pharmacovigilance in your country, how are the summaries of information from the system communicated to physicians and consumers (the general public)? Actively? Passively?
3. How are consumer reactions to medicinal drugs documented in your country?
4. Is there any interest in establishing a reporting system for consumer reactions to medicinal drugs in your country?
5. How can you and the organisation you represent contribute to establishing a reporting system for consumer reactions to medicinal drugs?

  Further **information** about the conference may be obtained from: Lena Westin or Jan Albinson, KILEN, Kammakargatan 7, S-111 40 Stockholm
  Tel: +46-8-69 60 100
  Fax: +46-8-69 60 110
  E-mail: kilen@kilen-institutet.se
  Internet: www.kilen.org

- The **VII World Conference on Clinical Pharmacology and Therapeutics of IUPHAR** - division of clinical pharmacology, and the **4th Congress of the European Association of Clinical Pharmacology and Therapeutics (EACPT)** will be held in Florence, Italy. 15-20 July, 2000
  For more information contact:
  Prof Giampaolo Velo
  Tel: +39-45-809 8611/807 4899
  Fax: +39-45-581111
  E-mail: cpt2000@sfm.univr.it

- The International Society for Pharmacoepidemiology (ISPE) will hold its **16th International Conference on Pharmacoepidemiology** in Barcelona, Spain, 20-23 August, 2000.
  For more **information** contact ISPE:
  Tel: +1-301-718-6500
  Fax: +1-301-656-0989
  E-mail: ispe@paimgmt.com

- The 8th Annual Meeting of the European Society of Pharmacovigilance (ESOP) will take place in Verona, Italy, 21-23 September, 2000.
  For more **information** contact:
  Prof Giampaolo Velo
  Tel: +39-45-809 8611/807 4244
  Fax: +39-45-581111
  E-mail: esop@sfm.univr.it

- The **Drug Information Association (DIA)** is organizing the following events of interest to drug safety and pharmacovigilance:

  - The DIA 36th Annual Meeting held in San Diego, USA, 11-15 June, 2000. One of the main themes is **Clinical Safety/Pharmacovigilance**.
  - A workshop on **Drug Safety Labelling** in Paris, France, 14-15 September, 2000
  - A training programme on **Medical Approach in Diagnosis and Management of Adverse Drug Reactions** in Paris, France, 12-13 October, 2000
  - A training programme entitled **Drug Safety Surveillance and Epidemiology** in Washington, USA, 23-25 October, 2000
  - A workshop on **Safety Information and Labelling** in New Orleans, USA, 4-5 December, 2000
  - A workshop entitled **Improving Pharmacovigilance Working Practices** to be held in Washington DC, USA, 11-12 December, 2000.

  For more **information** on the DIA events contact:
  Tel: +1-215-628 2288
  Fax: +1-215-641 1229
  E-mail: dia@diahome.org
  Or
  Tel: +41-61-386 9393
  Fax: +41-61-386 9390
  E-mail: diaeurope@stepnet.de

BOOKS *and other* PUBLICATIONS

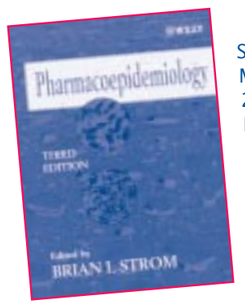
GUIDELINES FOR SETTING UP AND RUNNING A PHARMACOVIGILANCE CENTRE

In the mid-1990s, **Dr Martijn ten Ham**, then Chief of the Drug Safety Unit at WHO, Geneva, took the initiative to develop a guide to assist newcomers in the field of pharmacovigilance with the process of establishing and operating a centre for spontaneous adverse reaction reporting.

He asked Dr Ronald Meyboom, The Netherlands, who has long and broad experience in pharmacovigilance, to write a first draft. This draft was then subjected to review by consultative groups, meeting on two occasions in Geneva. Later on, the draft guide was sent to all National Centres participating in the WHO drug monitoring programme to ensure a broad acceptance of the text. After having gone through this thorough consultative process the guide has now been printed by *the* UMC.

This guide (25 pages) is a good basic text for use in teaching pharmacovigilance. It is distributed free of charge to all National Centres. If you would like a personal copy, please contact Anneli Lennartsson (anneli.lennartsson@who-umc.org) at *the* UMC.

PHARMACOEPIDEMIOLOGY



The 3rd edition of this standard reference textbook, edited by Brian Strom, University of Pennsylvania Medical Center, will be due in June 2000. The normal price is £120. Members of the International Society of Pharmacoepidemiology (ISPE) are offered a special price of £90. This book (880 pages) (ISBN 0471 89925 9) is published by John Wiley & Sons. Information may be requested from: John Wiley & Sons Ltd, 1 Oldlands Way, Bognor Regis, West Sussex, PO22 9SA, United Kingdom

Tel: +44-1243-843 294 Fax: +44-1243-843 296
E-mail: cs-books@wiley.co.uk
Internet: www.wiley.com

OPINION AND EVIDENCE: DRUG SAFETY

The 2nd edition of this book (with Ralph Edwards from *the* UMC as Guest Editor), is now available from ADIS International Ltd. It contains an analysis of drug safety trends, reports from international pharmacovigilance meetings, summaries of over 125 papers and an alphabetic drug database with reference to more than 2000 case reports of adverse drug reactions reported in the literature in 1999. The book is available at US$49.95 from:

ADIS books, Private Bag 65901, Mairangi Bay, Auckland 10, New Zealand

Fax: +64-9-4770787, *on-line order from* ***www.adis.com***

REPORTING ADVERSE DRUG REACTIONS - DEFINITIONS OF TERMS AND CRITERIA FOR THEIR USE

CIOMS (Council for International Organizations of Medical Sciences) recently published this book which includes 180 medical terms used in the reporting of adverse drug reactions representing 20 different system organ classes, based on the WHO adverse reaction terminology. For each term a *preamble*, providing comments that may be of help to validators of ADR reports, *a definition* and *basic requirements for use of the term* are provided. The book, including a CD-ROM version, is available at SF35 from CIOMS, c/o WHO, 1211 Geneva 27, Geneva, Switzerland.

IMMUNIZATION SAFETY

Issue number 2, 2000 (**78:** 153-280) of this bulletin produced by the World Health Organization has immunization safety as its special theme. Articles include the following:

- Immunization safety: a global priority (editorial). *M. Scholtz & P. Duclos*
- New challenges in assuring vaccine quality. *N. Dellepiane, E. Griffiths & J.B Milstein*
- Safety of immunization injections in Africa: not simply a problem of logistics. *M.Dicko, A.-Q.O. Oni, S.Ganivet, S.Kone, L. Pierre & B. Jacquet*
- Developing a national system for dealing with adverse events following immunization. *U.Mehta, J.B. Milstein, P.Duclos & P. Folb*
- Monitoring signals for vaccine safety: the assessment of individual adverse event reports by an expert advisory committee. *J.P. Collet, N. Macdonald, N. Cashman, R. Pless & The Advisory Committee on Causality Assessment*
- The vaccine safety datalink: immunization research in health maintenance organizations in the USA. *R.T. Chen, F. de Stefano, R. Davis et al*
- Simian virus 40, poliovirus vaccines and human cancer: research progress versus media and public interests. *J.S. Butel*
- Clinical safety issues of measles, mumps and rubella vaccines. *M.A. Afzal, P.D. Minor & G.C-Schild*
- Vaccine adverse events in the new millennium: is there reason for concern? *B.J. Ward.*

ADVERSE DRUG REACTIONS JOURNAL

In June 1999, the first issue of the Adverse Drug Reactions Journal (ISSN 1008-5734) was published in Chinese. The content page is translated into English. This quarterly journal is sponsored by the Beijing centre for adverse drug reactions monitoring. Chief Editor is **Dr Cheng Jinhua**. For subscriptions contact: Editorial Office, No 13 Ditan Park, Beijing 10011, P.R. China.

Introducing **ADR**espherics ...A new data-mining service

On a blue, cloudless spring day in Uppsala, Ralph Edwards talks about the new data-mining service which will be launched by *the* Uppsala Monitoring Centre (UMC) in July. This new data-mining service will be a major step forward and is central to the future direction of *the* UMC. Until recently, and in consultation with the National Centres, *the* UMC has used lists of outputs based on groupings (eg fetal malformation); and has added extra groupings which National Centres have suggested, such as 'new to system' ADRs. Now, there are over 2 million case reports to draw on, supported by human review. With such a massive amount of case information at *the* UMC, the universal need for advanced analysis tools is even more necessary.

"A fundamental objective of the WHO drug safety programme, at its inception in 1968, was to find an automated way of raising signals. Then the existing statistical software and computer power was very limited compared to today, and was not able to deal with heterogeneous data such as that provided by the National Centres." Even now, an automated system is only as good as the people who interpret and use the results. The regular ADR reports from all the 58 National Centres will, as always, provide the raw materials for data-mining. However, a new methodology for signal detection called Bayesian Confidence Propagation Neural Network, combined with the WHO database of ADRs will provide a powerful new capability for identifying ADR signals *(see box)*. The 'new approach' in data-mining will be able to say whether an ADR stands out from other drug/ADR combinations in the database and allow *the* UMC to analyse the nature of the association: influence of other drugs, age of patient and so on – all these associations can now be analysed. "This approach provides a different focus; with experience especially we will pick up some links earlier than before and pass them on to regulators. And, rather than having around 50 fields on case records, there will soon be 200 fields, allowing greater breadth of analysis. This will answer queries in a way we couldn't do before, as long as the fields are completed!"

this will be a huge benefit to all of us concerned with drug safety

Colleagues at regulatory authorities in the UK, Australia, the Netherlands and the USA are working on other approaches to the same problem. These approaches are adapted for national use, and some cannot deal with the analysis of the multiple data fields on case reports. "*the* UMC data-mining, to be called ADRespherics, will make this quality information and scientific analysis available to all countries participating in the WHO Programme, who will all benefit from the high-tech approach. Other scientists, researchers and clinicians may also be able to gain access to the data."

The service will also be made available commercially to pharmaceutical companies through *the* UMC. This is an extension of the current arrangements with the commercial sector, who have a right to information on early signals of their own products. As Ralph explains: "Early warning should result in better regulation in countries and companies. It is therefore natural and fair that we help Pharmacovigilance Managers in their work. There will be three levels of service available *(see box)*. When the service is launched this summer, drug companies won't be getting information that was not supplied before, but it will be better information and provide more analysis. Naturally, the usual confidentiality restrictions that currently exist will still prevail.

The 'new approach' in data-mining will be able to say whether an ADR stands out from other drug/ADR combinations

"Whilst the benefits of ADRespherics are many, all of us at *the* UMC want to stress the importance of understanding the limitations of this approach, which are common to all signal systems. A few associations the neural network will bring up, may not be real (they may be artefacts of the way the data is collected). Despite this caveat, there's no doubt that this will be a huge benefit to all of us concerned with drug safety, and assist in preventing drug disasters."

The world's largest ADR resource

Since 1978 *the* UMC has been the centre for independent global pharmacovigilance. Our ADR data resource is the largest and most comprehensive in the world, and is developed and maintained by *the* UMC on behalf of the World Health Organization. The data held is collected from the National Centres of 58 affiliate countries and comprises over 2,000,000 reports, to which 35,000 new reports are added quarterly. Many of the signals that prompt the National Centres to take action are generated by *the* UMC's clinical reviewers using this information.

A new and unique service

The combination of the BCPNN and the WHO database by *the* UMC has resulted in a powerful tool that is unique to pharmacovigilance. Now that capability is being made available to you for the first time through a new service called ADRespherics.

The primary objective behind ADRespherics is to give you the opportunity to monitor specific drugs to detect ADR signals as early as possible, so that your company has much more time and information to make the best decision about the continued use and labelling of a product. ADRespherics puts the power to know, and know early, at your disposal.

Three Flexible Services

Your specific needs are provided for with a portfolio of the following services:

1. **Cumulus - Data Mining Tables**
   This service allows you to track new drugs after launch, Cumulus provides you with ADR information from real patients to compare with your own research findings.
2. **Stratus - Selective Comparison**
   This service allows you to identify whether a drug has a specific problem that makes it stand out from others in its class.
3. **Nimbus - Customised Comparison**
   This service incorporates drug usage data in addition to raw numbers of spontaneous reports and allows for comparisons of reporting frequencies across countries and over time.

Proof of Concept

Retrospective test runs on the WHO database have shown that ADRespherics can detect signals earlier than other analytical approaches. Specifically, when ADRespherics was used to analyse reports on captopril the study found that its association with coughing would have been indicated as early as 1981, and strongly highlighted in summer 1983; in reality this signal was not reported until 1986 .

To find out more about ADRespherics please contact Mats Persson at *the* UMC.

Speed is essential these days. Now that the pharmaceutical industry markets globally, patients are exposed very quickly to new products, and therefore the world needs a way to analyse safety data as rapidly as possible. ADRespherics will help find this out at an early stage which enables regulators and scientists to begin closer scrutiny of the signal as soon as possible.

As Ralph explains, the new data-mining service ADRespherics is part of *the* UMC's long-term strategy: "Our ambition is to develop ways of distilling the information we are getting and linking it with other sources, so that researchers can go to one site and get all the relevant information rather than do a literature search, Internet search and other research work. We are actively exploring ways to assist National Centres and others to access pharmacovigilance information on one site." For people around the world, *the* UMC will harness the latest IT technology to speed up the process of signal analysis in order to give maximum assurance to patients and health professionals.

Our ambition is to develop ways of distilling the information we are getting and linking it with other sources

Why the name ADRespherics and the cloud formations? "While we're all enjoying the spring sunshine here we keep an eye out to see clouds on the horizon so that we can reach for our umbrella, raincoat and wellies in time. We chose the theme of clouds to illustrate the service as it shows the universal concern in the pharmacovigilance community to anticipate events, so as to have time to act. The name of the service will be ADRespherics to reflect the weather theme."

all National Centres will benefit equally from the new data-mining service

All systems of pharmacovigilance rely on the ADR information that comes in and *the* UMC needs your continued supply of ADRs! *the* UMC is part of a network, and all National Centres will benefit equally from the new data-mining service and will have access to the latest technology and first class analysis.

"None of us like stormy weather, but the latest developments here at *the* UMC give me confidence that we won't get caught without an umbrella in future."

Ethiopia

the UMC has received this report (below) from **Mr Gidey Amare**, Drug Administration and Control Authority, Ministry of Health, Ethiopia, describing the pharmacovigilance activities undertaken in his country:

Two workshops have been conducted so far.

The first workshop (a national one) was organized for professionals: working in teaching institutions; in medical professional associations; in regional health bureaux and hospitals.

The second one was organized for professionals mainly working in the inner city of Addis Ababa and referral hospitals.

In both workshops a total of 55 medical doctors, 44 pharmacists, 3 pharmacologists, 1 epidemiologist, 10 pharmacy technicians and one health officer participated. Both the workshops were successfully completed as planned. The participants attended the workshops with great interest and active participation. Generally speaking the performance and participation were beyond our expectations. Participants strongly recommended such workshops to be conducted to introduce professionals, working at different levels and regions, to the concepts of pharmacovigilance and thereby establish a functional ADR monitoring system in the country.

We are planning to continue with the *awareness creation campaign* if our scarce resources allow us. We believe that the efforts to disseminate the information on the need to establish ADR monitoring should at least cover the major regional national states. We plan to conduct three regional training workshops before the end of our fiscal year using the individuals who participated in the national workshop as a bridge to facilitate the administrative arrangements.

We have already developed an ADR reporting form and are now in the process of arranging and discussing with the postal service to print postage prepaid ADR reporting forms, to facilitate reporting. We have also reached agreement that a division responsible for ADR monitoring will be established within the organizational structure of the drug administration and control authority.

I was working in the task force formed to prepare a draft of the functions, responsibilities and organizational structure for the authority. This gave me a good opportunity to convince the task-force to consider ADR monitoring as one of the main functions of the authority. At this level it is fully accepted. What's left now is approval by the office of the Prime Minister. Hopefully it will be approved!

the UMC would like to thank Mr Gidey Amare for his contribution and wish him continued success! We always welcome individual reportage (and photographs) from National Centres, so please do send us your material!

Peru

A national technical committee on pharmacovigilance, coordinated by the Ministry of Health, has started implementing a national pharmacovigilance system for Peru. A reporting form and promotional material have been developed and distributed throughout the country. The first case reports have been received from the medical profession and from pharmaceutical companies. Pharmacovigilance training courses for health professionals are being planned.

Activities are coordinated by **Dr Susana Vasquez**, Centro Nacional de Farmacovigilancia Informacion de Medicamentos, Direccion General de Medicamentos, Insumos y Drogas, Ministerio de Salud, Peru.
Tel: +51-14-716246
Fax: +51-14-716353
E-mail: cenafim@digemid.gob.pe

The Netherlands

Dr Arthur P. Meiners, Head of Pharmacovigilance at the Medicines Evaluation Board in The Netherlands recently launched an initiative to develop an open-source software for management of adverse reaction data, compatible with the latest standards recommended by ICH (International Conference on Harmonization). Here is a summary of his reasoning and project proposal:

POSISYS project announcement 2000.02.19 (the pharmacovigilance/pharmacoepidemiology open source initiative system)

Nearly all pharmacovigilance / pharmacoepidemiology software systems currently in use by regulators, pharmaceutical companies and academia are either commercial products with specific extensions requested by the buyers, or home grown products. For commercial companies the buyers are relatively few. The fact that most systems are relatively unique increases the cost of maintenance and updating. These factors are seriously limiting the speed with which new standards are implemented, and the high cost of systems limits their availability to smaller organisations and developing regions.

The growing success of the free, unix compatible, operating system, Linux, clearly indicates that the Internet allows a different approach to systems development. One which is based on collaborative effort and results in highly standardised, high quality systems which can be obtained and used by all free of charge. Under such conditions commercial companies can still offer many additional quality services, but they cannot dictate the cost or speed of progress any more.

In view of the above, I propose to develop the *posi-system*, the Pharmacovigilance (/epidemiology) open-source initiative system, to be based on international open standards, and to be made available free of charge to any interested party. Of course, I cannot develop such a complete system alone within a reasonable period of time. Help is clearly needed!

Help can be in the form of submission of useful routines any of the readers of this article have developed and are allowed to submit as freeware under the general public license. Help can take the form of testing and documenting the posi-system as it develops. Or, it can be help in hosting one or more web-servers to and from which the project components can be up/downloaded. The current POSISYS website **(http://home.planet.nl/~ameiners/posisys.html)** is a private site. Please note also, that this is a non-profit effort, to which direct financial support is currently not possible. But all other support from any interested parties is welcome.

If you are interested in supporting this project, please fill in and submit the POSISYS project response form located at:

http://home.planet.nl/~ameiners/posisys/posisys_proj_reply.html

Dr Arthur P. Meiners
Tel: +31-70-356 7400
Fax: +31-70-356 7515
E-mail: a.p.meiners@planet.nl.

New member Countries!

In March, *the* UMC received the first contributions of adverse reaction reports from Cyprus and the Federal Republic of Yugoslavia. Both countries had previously submitted their formal applications for becoming members of the WHO International Drug Monitoring Programme and they have now fulfilled the requirements.

The WHO International Drug Monitoring Programme now includes *58 full-member countries*. Five countries are awaiting full membership status while the issue of technical compatibility with the WHO reporting requirements is being resolved.

Correspondence with the new Centres should be directed to:

Federal Republic of Yugoslavia
Prof Vaso Antunovic
Clinical Centre of Serbia
National Centre for Adverse Drug Reactions
Visegradska 26
Yu-11000 Belgrade
Yugoslavia, Fed Rep of

Tel: +381-11-361 5531
Fax: +381-11-361 5630

Cyprus
Dr Athos Tsinontides
Clinical Pharmacist
Drug Information
& Poison Control Centre
Lefkosia General Hospital
Lefkosia
Cyprus

Tel: +357-236 9005
Fax: +357-247 7194
E-mail: dipcc@cytanet.com.cy

Here is a description of the pharmacovigilance system in Cyprus:

The Department of Pharmaceutical Services of the Ministry of Health established the Cyprus Pharmacovigilance Program in 1997. It was developed in conjunction with the Drug Information and Poison Control Centre (DIPCC).

The computer and communication resources and library services are shared with the DIPCC, which minimized infrastructure costs and allowed the Program to operate almost immediately after its establishment.

The adverse drug reaction (ADR) reporting form was prepared based on the WHO reporting form and is produced in Greek and English. The form was initially sent to all physicians, dentists and pharmacists accompanied with a letter explaining the goals of the program. Similar information was sent to the National Medical, Dental, Pharmaceutical and Nursing associations. In all communications we emphasized the WHO and EU support to such programs and their role in drug safety.

Stimulation for reporting is pursued through:

a) the newsletter *Clinical Pharmacy News*

b) by mailing the ADR form to healthcare professionals at regular intervals

c) through presentations of the program to organized groups.

The newsletter is published by the division of Clinical Pharmacy four times a year and deals with drug and poison information as well as pharmacovigilance issues. Pharmacovigilance issues usually include the presentation of interesting local or internationally reported cases.

An ADR form is sent along with the newsletter, which is distributed for free every three months to all physicians and pharmacists in Cyprus.

In our effort to involve as many healthcare professionals as possible and as there is currently no Medical or Pharmacy School in Cyprus, we approached the Nursing School Director of Education, who agreed that nurses can play a major role in ADR surveillance. She promised to incorporate a series of lectures on Pharmacovigilance in the Nursing School curriculum.

Currently there is no legislation for ADR reporting in Cyprus. This, however, will change soon as the Cyprus legislation is being revised and will be harmonised with the European legislation in view of the accession of Cyprus to the European Union.

Since the beginning of the Program, 60 reports have been received. The reports are evaluated by the staff of the Division of Clinical Pharmacy and an oral or written feedback is provided to the reporter.

Serious reports are forwarded to the Drug's Council, which is the regulatory authority that governs the use and licensure of all drugs in Cyprus. The 1997 reports were submitted to the WHO Collaborating Centre in March 2000 and full membership to the WHO Drug Monitoring Programme is expected soon.

The future plans of the Program include a nationwide campaign for the promotion of pharmacovigilance that will include the production of a poster, an improved design of the ADR form and lectures to all government hospitals for the year 2001.

Dictionary
Users' Group Meeting

The latest WHO dictionaries users' group meeting was held at the DIA meeting in Philadelphia, USA. During this meeting, **Professor Peter Murray-Rust** presented XETER, a web-based software to be used for browsing, searching and comparing different terminologies and versions of terminologies.

For further **information** on the users' group, please contact **Liza Storm** at *the* UMC, or visit our website on: **www.who-umc.org**

The Internet training course regarding adverse reaction terminology and the drug dictionary will be launched within 6-8 weeks. We will send you further information about this in due course.

Product News

The new versions of the computerized **Drug Dictionary** and **Adverse Reaction Dictionary**, containing the first quarter of 2000, are now available. In this version of the Drug Dictionary we have also included the revised ATC-codes.

The new paper print of the Drug Dictionary (ed. March 31, 2000) will be ready during July 2000.

People *and* Places

CIOMS

In December 1999, **Dr Zbigniew Bankowski** retired from his post as Secretary General of CIOMS (Council for the International Organizations of Medical Sciences). During the last fifteen years CIOMS has, under the leadership of Dr Bankowski, made important contributions to progress in the science of pharmacovigilance particularly by convening a great number of meetings and publishing a series of influential monographs on various drug safety related subjects.

Turkey

In February 2000, **Ms Sevgi Öksüz** retired from her position as head of the national pharmacovigilance centre in Turkey after having served at the Ministry of Health for 25 years. Ms Öksüz was the main organizer of the 22nd Annual Meeting of Representatives of National Centres, held in Ankara in September 1999. She is still active in the scientific committee of ESOP (European Society of Pharmacovigilance).

USA

In February 2000, it was announced that **Dr Peter Honig** has been appointed Director of the Office of Post-Marketing Risk Assessment (OPDRA) at the FDA Center for Drug Evaluation and Research. He has worked for the FDA since 1993 and became Deputy Director of OPDRA in October 1999.

India

Professor (Mrs) **Nilima A. Kshirsagar**, Head of the Special WHO Centre on Pharmacovigilance in Mumbai, India, has been appointed Dean of the T.N. Medical College. She has moved her Department of Clinical Pharmacology from the Seth G.S. Medical College and K.E.M Hospital to her new base, now at:

T.N. Medical College & BYL Nair Hospital
Dr Al Nair Road
Mumbai Central
Mumbai (Bombay) 400 008, India

Tel: +91 22 308 5379, 308 1490/91/92/93
Fax: +91 22 307 5243
E-mail: dclphkem@bom7.vsnl.net.in

New Zealand

Dr Michael Tatley recently joined the New Zealand National Centre in Dunedin as a Medical Assessor. He came to the centre from Cape Town, South Africa.

Tanzania

Mr Henry Irunde has left the National Centre at Tanzania Drug and Toxicology Information Service, to take up new studies. The current contact person is:

Ms Mary Masanja
Tadatis
Pharmacy Board
PO Box 77150
Dar-es-Salaam, Tanzania

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