

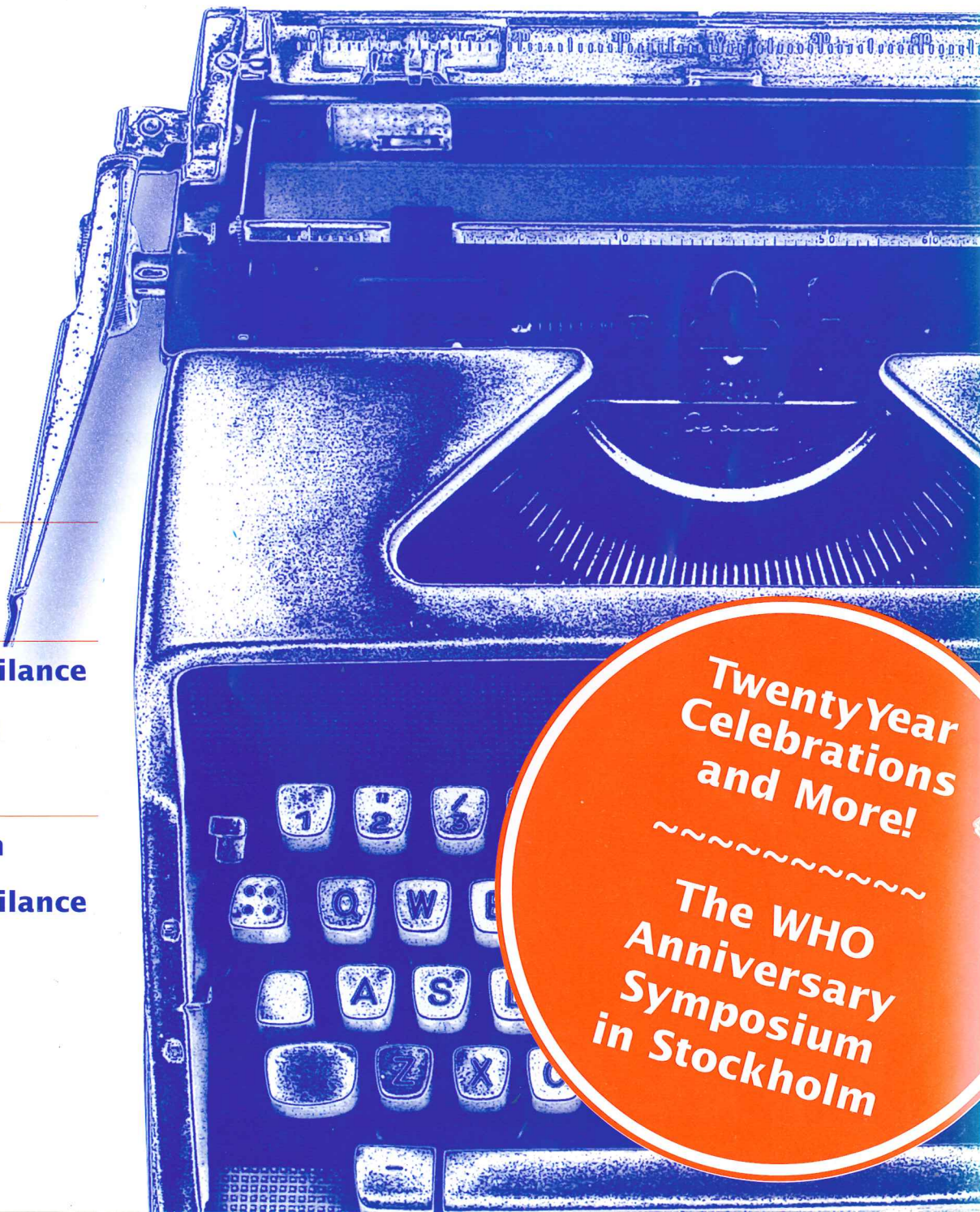


Uppsala

REPORTS

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

- **Anniversary Symposium**
- **New Member Countries**
- **Pharmacovigilance in Sudan and Argentina**
- **PhD thesis in Pharmacovigilance**

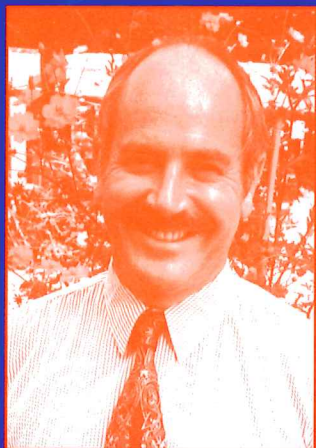


Twenty Year Celebrations and More!

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**The WHO Anniversary Symposium in Stockholm**

## MESSAGE FROM RALPH EDWARDS, DIRECTOR



We are very lucky to have had Ana Maria Corrêa-Nunes working with us recently. Ana Maria is from INFARMED, the Ministry of Health, Portugal, and has spent a two month sabbatical leave here in Uppsala (see photo on next page)

Ana Maria has been actively involved in developing the material gathered from the first CIOMS Communications Working Group, which met in Dublin last year. We intend to make drafts of the papers available on the Internet very soon, so that we can gather your comments and edit them further. We will then write the Good Practice Guidelines and publish these as a CIOMS monograph, probably later this year. All in all, this is really a very exciting stage in our efforts to push good communications practice high up the agenda in the field of pharmacovigilance.

In another aspect of her work with us, Ana Maria has reviewed how we process international data to generate signals. This follows our successful introduction of neural network data-mining, which we have been working on for some time. We are confident that the results will be interesting and provide more efficient ways of involving National Centres and our panel of experts in generating signals. Our aim is to reduce list-processing and to offer statistically outstanding information on new adverse drug reactions.

You'll find more information about our twenty-year celebrations on this page. I do hope we shall have the pleasure of seeing many of our international friends in Sweden in December to celebrate with us - and to take part in an extensive professional debate. Do join us!

Best wishes,

**I Ralph Edwards**

# 20 Year Celebrations and more!

**We are very pleased to announce that we are holding a WHO Anniversary Symposium in Stockholm 9 - 10 December, 1998.**

**Entitled: *The Current State of Pharmacovigilance - A Critical Examination.***

The programme will focus on four subjects:

- ***Spontaneous Reporting***
- ***Special studies in Pharmacoepidemiology***
- ***Benefit/Risk assessments***
- ***Communications in Pharmacovigilance.***

The structure will be based on classical logic. There will be one presentation of the strengths and opportunities (thesis), one of the weaknesses and threats (anti-thesis) followed by a concluding session (synthesis).

The anniversary symposium, which is reserved for scientific debate, will be followed by a one-day conference on 11 December at which representatives of regulatory authorities will present their perspectives on the four selected subjects.

**As well as generating important professional debate, this symposium is an excellent chance to celebrate no less than three anniversaries:**

- ***50th Anniversary of the WHO***
- ***30th Anniversary of the WHO Drug Monitoring Programme***
- ***20th Anniversary of the WHO Collaborating Centre - the UMC, Uppsala***

**We look forward to welcoming colleagues from around the world to this special event.**

We have commissioned IIR Ltd to take care of all practical arrangements for the symposium. Invitations will be distributed in the near future by IIR. If you want to make sure you get an invitation, please contact:

Anouk Cruttenden, IIR Ltd

Tel: +44-171-9155076

Fax: +44-171-8505001

E-mail: [acruttenden@iir-conferences.com](mailto:acruttenden@iir-conferences.com)

or Sten Olsson at *the Uppsala Monitoring Centre.*

# NEWS FROM *the* UPPSALA MONITORING CENTRE



## NEW TEAM MEMBER MAKES IT 18!

*Malin Ståhl* has joined the Uppsala team, bringing the group to 18 members. Malin Ståhl is a Biomedical Scientist and is working on Signal Development and other projects.

Our most recent group photo shows almost the full team. It was taken during our Strategic Planning Week in May at Haga Slott, a beautiful old Swedish castle. It is always difficult to get us all in the one place at any one time, but on this occasion we managed to get 17 out of 18, which wasn't bad! (Only Monica Petterson is missing - absent on maternity leave).

*Ana Maria Corrêa-Nunes* INFARMED, the Ministry of Health, Portugal. Working temporarily at *the* UMC.



Malin Ståhl



Ana Maria Corrêa-Nunes

♦ 17 members of *the* UMC team

## SIGNAL DEVELOPMENT PROJECT

A working group at *the* UMC has begun reviewing signal detection and evaluation. One of the goals of the Centre is to maximize the usefulness of the WHO database in detecting signals, and we are constantly evaluating new ways of doing this. We have previously mentioned our new methodology for detection of drug adverse reaction associations, which uses a data-mining technique based on Bayesian statistics (see **Recent Publications** for further details). We are also collaborating with IMS, who hold drug usage and prescription data. So it seemed appropriate to look at the signal process with these in mind.

From our own discussions we have a vision of what we can provide to you, our worldwide colleagues. But to ensure that we really deliver the service you require, we need as much feedback as possible.

We hope this project will enable us to provide several new products, which will also be available to industry colleagues and will help to fund the rest of our new improved signal analysis and detection procedure.

We will provide more details at the WHO National Centres annual

meeting in Tokyo in September. Afterwards, we will distribute a questionnaire to all National Centres and industry, through which we will be able to collect the information we need to refine the proposed signal process based on your views.

## NEW INTERIM BOARD APPOINTED FOR *the* UMC

A new interim Board to oversee the affairs of *the* UMC was recently appointed. The Chairman is Alf Nilsson. This follows Swedish Government queries about technical accounting issues at the Centre (the Swedish Government provides core funding for the Centre). There is no question about the financial probity of the accounts or of the misuse of funds, and we hope these queries will be resolved quickly.

## WHO DICTIONARIES USERS' GROUP MEETING

This year's first WHO Dictionaries Users' Group meeting was held at the Annual DIA meeting in Boston on 8 June.

Marie Lindquist, Ralph Edwards, Mats Persson and Anna Lindquist attended from *the* Uppsala Monitoring Centre.

Our new projects: Neural Network

Data-Mining; Analysis with drug utilization data from IMS, ICD-WHOART amalgamation; The New WHO Drug Dictionary, DD changes/frozen databases and the New Adverse Reactions Database - were presented by Marie Lindquist.

Further information and minutes from the meeting can be found at our website homepage (<http://www.who-umc.org>).

The next Users' Group meeting will be held at the DIA Clinical Data Management meeting in Berlin, Germany, 26 October, 1998.

## CURRENT EDITIONS OF THE WHO DICTIONARIES

The current computerized editions of the Drug Dictionary, DD Access (Standard version) and Adverse Reaction Terminology contain information up to and including the second quarter of 1998.

The new paper-print edition of the Drug Dictionary, (dated 31 March, 1998) containing the new ATC-codes, is currently available from *the* UMC.

New updated versions of the paper-print English, German, French and Portuguese Adverse Reaction Terminologies are also currently available.



# COURSES & MEETINGS

in PHARMACOVIGILANCE

## COURSES

■ **The National ADR Monitoring Centre in Malaysia** is organizing a national conference with invited guests from the ASEAN region, taking place on 12-13 October, 1998.

For more information please contact:

**Ms Abida Haq**  
Tel: +60-3-7573611  
Fax: +60-3-7562924  
E-mail: ah@bpfk.gov.my

■ **Pharmacovigilance Training Course in the Eastern Mediterranean Region** on 16-18 October, 1998. (This course will probably be held in Rabat, Morocco).

For more information please contact:

**Dr A. Alwan, Director, Health Services Department, WHO, EMRO**  
Tel: +20-3-483 0090/96/97/99  
Fax: +20-3-483 8916

■ **An International Workshop on Adverse Drug Reaction Monitoring** will be held at J.N. Medical College, Aligarh, India on 9-12 November, 1998.

For more information please contact:

**Professor K.C. Singhal**  
Tel: +91-571-400584  
Fax: +91-571-508013

■ **A course on Adverse Drug Reactions** is being organized by Healthcare Education Services Ltd, Edinburgh, UK on 1-2 December, 1998.

For more information please contact:

**Health Education Services Ltd**  
Tel: +44-131-557 2477  
Fax: +44-131-557 6778

■ **International Training Course in Adverse Reactions and ADR monitoring** at the Uppsala Monitoring Centre, Uppsala, Sweden. We have decided to postpone this two week training course until May, 1999. Invitations will however be distributed well in advance.

For more information please contact:

**Sten Olsson at the UMC**

## MEETINGS

■ **The DIA** is holding a workshop on *Monitoring Drug Safety - A Shared Responsibility* at the State Institute for Drug Control in Prague, Czech Republic on 7-8 September, 1998.

For more information please contact:

The Drug Information Association, USA  
Tel: +1-215-628 2288, Fax: +1-215-641 1229  
E-mail: dia@diahome.org

■ **IIR Ltd**, is organizing a conference on, *Optimizing & Improving Pharmacovigilance & Benefit/Risk Assessment* at One Great George St, London, UK on 15-16 September, 1998. A pre-conference briefing on, *Developing Strategies for Successful Signal Generation* will be held on 14 September and a post-conference workshop on *Examining Causality Assessment* on 17 September.

For more information please contact:

Anouk Cruttenden, IIR Ltd  
Tel: + 44-171-915 5076, Fax: + 44-171-850 5001  
E-mail: acruttdenden@iir-conferences.com

■ **The DIA** is holding a seminar on, *Medical Approach in Diagnosis and Management of ADRs* at the Hotel Sofitel Paris Forum Rive Gauche, Paris, France on 24-25 September, 1998.

For more information please contact:

The Drug Information Association - European Office  
Tel: +41-61-386 9393, Fax: +41-61-386 9390  
E-mail: diaeurope@stepnet.de

■ **The European Society of Pharmacovigilance (ESOP)** is organizing its sixth annual meeting at the Hotel Bara, Budapest, Hungary on 28-29 September, 1998.

For more information please contact:

János Borvendég or Sándor Elek,  
The National ADR Monitoring Centre  
Tel/Fax: +36-1-215 8977

■ **Nordic Vaccine Meeting 1998 - Focus on Surveillance and Vaccine Research** at the Congress Hotel Majvik, Kirkkonummi, Finland on 7-8 October, 1998.

For more information please contact:

Kari Lankinen (Chairman, organizing committee)  
Tel: +358-9-4744 8667, E-mail: kari.lankinen@ktl.fi  
Nordic Vaccine Meeting, Secretariat  
Fax: +358-9-4744 8675

■ **IBC** is organizing a conference entitled: *Clarifying Current International Regulatory Reporting Requirements for Adverse Drug Reactions* at One Whitehall Place, London, UK on 27-28 October, 1998. A pre-conference workshop on: *Selecting, Implementing and Managing Information Systems to Effectively Meet Reporting Requirements for ADRs* will be held on 26 October at Café Royal, London, UK.

For more information please contact:

Laura Viberti at IBC  
Tel: +44-171-453 5496, Fax: +44-171-636 6858  
E-mail: cust.ser@ibcuk.co.uk

## FORTHCOMING PUBLICATIONS

**I**N September this year we plan to publish the report on the International Conference on *Effective Communications in Pharmacovigilance*, held last September in Erice, Sicily. This is currently being printed in Kumasi, Ghana and you will be able to obtain a copy from the Uppsala Monitoring Centre. Participants in the conference will receive their own copies automatically.

The second edition of *National Pharmacovigilance Systems* is also due to be published in September. Following detailed updating of the Country Profiles data, the second edition will contain a very comprehensive collection of individual country information. It will have profiles from 57 countries, with 12 new countries and 2 new vaccine centres. For more information contact Sten Olsson at the Uppsala Monitoring Centre.

**PhD thesis on Pharmacovigilance.** Dr Ronald Meyboom, the Netherlands.

Ronnie Meyboom has prepared a PhD thesis on signal detection in pharmacovigilance. The aim of this work is to improve our understanding of the scientific processes underlying the early warning function of *spontaneous reporting*, and to help improve efficiency and reliability in pharmacovigilance.

The thesis begins with a retrospective analysis of a large number of subsequent drug-related problems encountered by the (former) Dutch pharmacovigilance centre. Study targets were the characteristics of the drugs, the problems involved and the composition

of the data constituting signals. A general review follows on what signals are, where they can be found, why something is likely to be a signal and why not, and signal management.

The thesis looks in detail at the role of standardized case causality assessment. In the final chapter the various findings and views are put into perspective and an attempt is made to glimpse future developments and changes in pharmacovigilance and the study of approved medicines. The thesis contains a lot of information of potential value in improving pharmacovigilance globally.

The supervisors are clinical pharmacologist, Professor Frank Gribnau, and clinical pharmacist, Dr Chiel Hekster, of the Nijmegen University Hospital. Professor Ralph Edwards has been invited to contest the thesis which will be defended on Tuesday 13 October at the Nijmegen University.

The thesis will be published in book form by the Netherlands Pharmacovigilance Foundation (LAREB) and is currently available. It will be distributed by LAREB to all national centres. You can obtain additional copies from LAREB:

Goudsbloemvallei 7,  
5237 MH Den Bosch,  
The Netherlands  
Tel: +31 (0)73 646 9700  
Fax: +31 (0)73 642 6136  
E-mail: info@lareb.nl

## RECENT PUBLICATIONS

### Dictionnaire de Pharmacovigilance Médicale

This is the second edition of a dictionary, compiled by Dr Pierre Biron, Department of Pharmacology, University of Montréal, Canada. It has explanations of all the most common words and concepts used in pharmacovigilance and pharmacoepidemiology. It is a 215 page document written in French, with all technical terms translated into English.

Send your order to:

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### From the UMC

#### the Uppsala Monitoring Centre

A.Bate, M. Lindquist, I.R. Edwards, S. Olsson, R. Orre, A. Lansner, R.M. de Freitas, *A Bayesian neural network method for adverse drug reaction signal generation*. European Journal of Clinical Pharmacology. (1998) 54(4):315-321

S. Olsson, *Role of WHO Programme on International Drug Monitoring in Co-ordinating Worldwide Drug Safety Efforts*. Drug Safety. (1998) 19(1):1-10

M. Lindquist, *The WHO Programme for International Drug Monitoring: The Present and Future in Mitchard M (ed) Electronic Communication Technologies; A Practical Guide for Healthcare Manufactures*. Buffalo, Interpharm Press (1998) 527-550



# News from Around the World

## PHARMACOVIGILANCE DEVELOPMENT IN SUDAN

Monitoring medical drugs is no longer the exclusive concern of wealthy countries. Around the world, countries in different phases of development have proliferating drug markets that need to be monitored.

In these countries, both governmental and private channels for drug distribution may exist and many potentially toxic, traditional, non-orthodox products may be in use.

Ronnie Meyboom from the Netherlands had a pleasant start to this year, making a two-week consultancy-visit to Sudan in January. He went on behalf of the WHO Regional Office in Alexandria (EMRO). He has kindly summarized his impressions for *Uppsala Reports*.



### Current position

Sudan is a large country in northern Africa with a mixed population. It has a comparatively small and densely populated urban area around the capital, Khartoum. This is where the healthcare infrastructure and medical and pharmaceutical expertise are concentrated. In the large, remote and scarcely-inhabited areas, healthcare provisions can be difficult to find, although a large network of primary-care stations exists throughout the country.

Sudan already has a well-designed regulatory system, guided by an authoritative Technical Committee. The Directorate of Pharmacy of the Ministry of Health, and the Faculties of Medicine and Pharmacy of Khartoum University are also well developed institutions.

In Sudan there is, a rapidly expanding private market for Western drugs, which are sold in the many retail pharmacies, especially in towns. Because medical care is expensive, many people use drugs recommended by the pharmacists. Consequently, where adverse reactions occur, doctors may not know what drugs have been taken.

### Endemic Disease

Sudan is also suffering from long-lasting civil strife. After malnutrition, morbidity in Sudan is dominated by endemic infectious diseases such as malaria, infectious diarrhoea, tuberculosis, leprosy, leishmaniasis and bilharzia, all requiring treatment with potentially toxic drugs. The long treatment regimes often needed for these diseases may not be feasible, leading to occurrences of therapeutic failure, adverse reactions and resistance development.

Other factors of potential relevance in Sudan are:

- Genetically or environmentally determined adverse reactions (e.g. G6PD deficiency)
- Problems relating to traditional remedies, such as adverse effects, interactions (e.g. karakadee, aradeb) and inefficacy
- Non-compliance (wrong indication, dose, duration or route)
- Availability and affordability of essential drugs
- Rational budgetary spending
- Misleading promotion in the community
- Adverse effects of repellants against disease spreading vectors (e.g. gammexane)
- Transport and storage of drugs under harsh conditions.

### Proposals

Pharmacovigilance in Sudan could be started as a regional activity in an environment where it is most likely to succeed, such as the university hospital in Khartoum. Similar activities can then be introduced at other interested hospitals throughout the country, in collaboration with the established centre and using the same methodology. It needs to be made clear from the beginning that pharmacovigilance is a national (i.e. federal) activity, for and by all healthcare practitioners and institutes throughout the country.

Pharmacovigilance could be developed in combination with poison control as well as drug information and pharmaceutical care.

Pharmacovigilance is also more likely to succeed if there is simultaneous investment in therapeutics education. A concrete design for a training program for pharmaceutical and medical professionals has been provided to EMRO.

Given the many competent and dedicated people working at the Directorate of Pharmacy, the universities and elsewhere in the healthcare system, we can expect that pharmacovigilance will thrive and develop into a useful tool for improving the rational and safe use of medical drugs in Sudan.

## REPORT ON THE PHARMACOVIGILANCE PROGRAMME FOR THE NORTHEAST OF ARGENTINA

*Dr Mabel Valsecia, Chief of Regional Centre of Pharmacovigilance, Associate Professor of Pharmacology, National Northeast University - School of Medicine, Corrientes, Argentina.*

Mabel Valsecia has been involved in research covering the first three years of implementation of the Pharmacovigilance Programme of the Department of Pharmacology, the National Northeast University School of Medicine, Corrientes, Argentina. This is a node of the

National System of Pharmacovigilance of the National Administration of Drugs Food and Medical Technology (ANMAT).

Pharmacovigilance studies in Argentina are few and limited. Before this study there had been no studies at all in the northeast region.

## Drug-Induced Pathologies

The study was based on 900 voluntary ADR reports received from five states in the northeast of Argentina. Reports were also received from Asuncion, capital of Paraguay. Reporting revealed a significant incidence of severe drug-induced pathologies. Etiological investigations were carried out to test drug-related and/or non-drug causes, in order to provide therapeutic advice regarding the incriminated drugs.

The study used the reports from the National System of Pharmacovigilance for spontaneous reporting. Several hospitals and health centres throughout the northeast region sent in ADR reports. Physicians and other healthcare personnel then received relevant information from the reporting centre to assist them in treating patients with drug-induced diseases.

Feedback information from the reports is published as pharmacovigilance bulletins in postgraduate course journals. All individual reports are analyzed, coded and then sent on to the National Pharmacovigilance Centre. The relevant information is then forwarded to the Uppsala Monitoring Centre, Sweden.

## Outcomes

The study showed that 83% of the reports came from physicians, 12% from medical students, 3% from physiotherapists and the rest from pharmacists, dentists, nurses and consumers.

75% of the ADRs were of type A: predictable and dose-related, mainly an extension of the pharmacological effects, drug interactions, side effects and direct toxicity. The rest were of type B: unexpected and unpreventable, such as anaphylactic reactions, allergic vasculitis or hepatitis. 30% of the ADRs were classified as being due to irrational prescribing with half of them attributed to medical negligence. The adverse reaction was classified as mild in 16%, moderate in 50% and serious in 14% of cases (12 fatal). 16% of these required pharmacological treatment and 5% resulted in hospitalization.

## New Signals

The ADR reporting programme identified previously unrecognized signals (e.g. night terror associated with Oxybutynin). ANMAT obtained this information about Oxybutynin and passed it on to the Uppsala Monitoring Centre.

*Some of the major conclusions drawn from the study are:*

- The detection of a significant incidence of severe drug-induced pathologies
- Confirmation of the need for therapeutic drug monitoring and the extension of pharmacovigilance related studies
- The need for educational intervention, both at under- and postgraduate level, to improve the rational use of drugs.

More than anything the study shows that the Pharmacovigilance Programme needs to expand in Argentina and in Latin America.

## EUROPEAN UNION PRINCIPLES FOR PROVIDING THE WHO WITH PHARMACOVIGILANCE INFORMATION

In January 1998 the Committee for Proprietary Medicinal Products (CPMP), Pharmacovigilance Working Party discussed and agreed Principles for providing the WHO headquarters in Geneva and the WHO Collaborating Centre for International Drug Monitoring in Uppsala with pharmacovigilance information.

*The Principles were agreed under the following headings:*

- Adverse Drug Reaction Reports
- Rapid Alerts
- Infofaxes
- Other Pharmacovigilance Information for Centrally Authorized Products
- Outcomes of Referrals
- CPMP Position Statements on Pharmacovigilance Issues

In addition, Member States will provide further information for nationally authorized products according to their legislation and agreements.

*The Principles, available in document CPMP/PhVWP/053/98, may be obtained from the Uppsala Monitoring Centre.*

## NATIONAL CENTRES ANNUAL MEETING

**The 21st Annual Meeting of National Centres Participating in the WHO Programme for International Drug Monitoring will be organized in Tokyo, by the Ministry of Health & Welfare, Japan, on 7-10 September, 1998.**

**For more information contact: Dr Martijn ten Ham, WHO, Geneva:**

**Tel: +41-22-7913638 Fax: +41-22-7914730 E-mail: [tenhamm@who.ch](mailto:tenhamm@who.ch)**

**ESTONIA, IRAN and ZIMBABWE** have now started to submit ADR reports to the Uppsala Monitoring Centre and have thus fulfilled all criteria for becoming full members of the WHO Programme, which now has 53 members. **MEXICO** and **VIETNAM** have recently applied for membership of the programme. During the last year 6 countries have joined the programme and an additional 4 have applied for membership.

### Communications details for the new national centres:

#### ESTONIA

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E-mail: cpfeum@mpsnet.com.mx

#### VIETNAM

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Adverse Drug Reaction Centre  
Institute for Drug Quality Control  
Ministry of Health, 48 Hai Ba Trung Street, Hanoi  
Tel: +84-4-245292  
Fax: +84-4-8231253

#### BRAZIL

In February 1998, the Instituto da Criança, Sao Paulo, headed by Dr Anthony Wong, was designated as a Reference Centre for the Development and Promotion of Pharmacovigilance, within the WHO Program for International Drug Monitoring. The Institute is actively involved in establishing and promoting pharmacovigilance in Brazil.

### the Uppsala Team



**Director:**  
**Manager (External Affairs):**  
**Manager (Internal Affairs):**  
**Manager (Marketing):**  
**Manager (Research & Development):**  
**Sales & Promotions Manager:**  
**Scientists:**

#### Pharmacists:

**External Affairs Assistant:**  
**Internal Affairs Assistant:**  
**Sales Assistant:**

Professor Ralph Edwards  
Sten Olsson  
Cecilia Biriell  
Liza Storm  
Marie Lindquist  
Mats Persson  
Mohamed H. Farah (*Traditional Medicines*)  
Jonathan Edwards (*Information Systems*)  
Malin Ståhl (*Biomedical*)  
Andrew Bate (*Neural Network Methodology*)  
Helena Fucik  
Monica Pettersson  
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**Internet:** <http://www.who-umc.org>