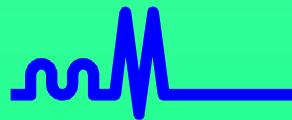


WHO Collaborating Centre for International Drug Monitoring

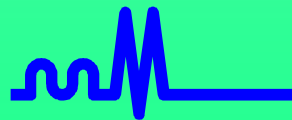
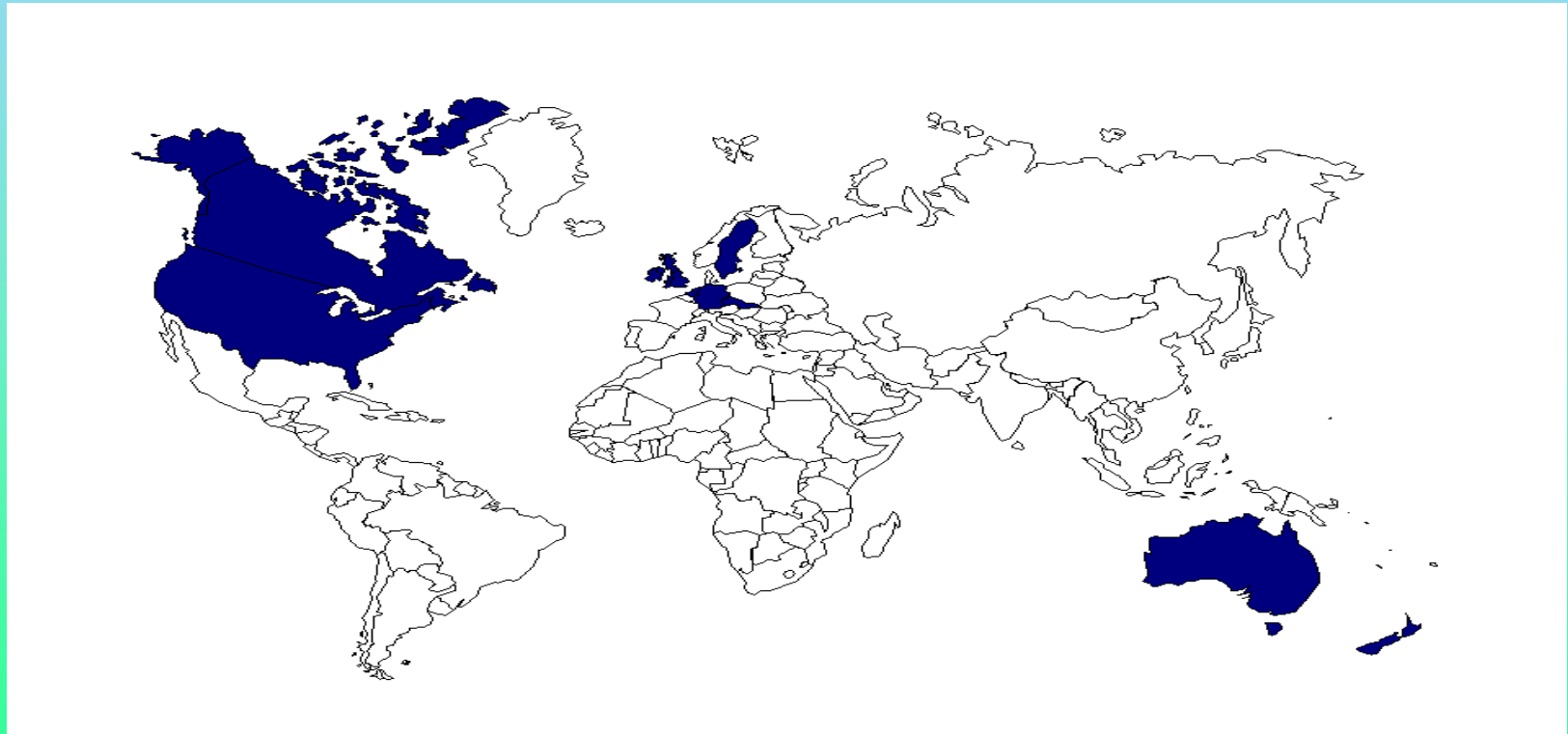


the Uppsala Monitoring Centre
www.who-umc.org



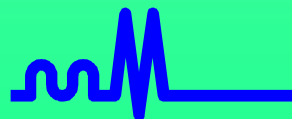
WHO Drug Monitoring Programme

Founding Members 1968

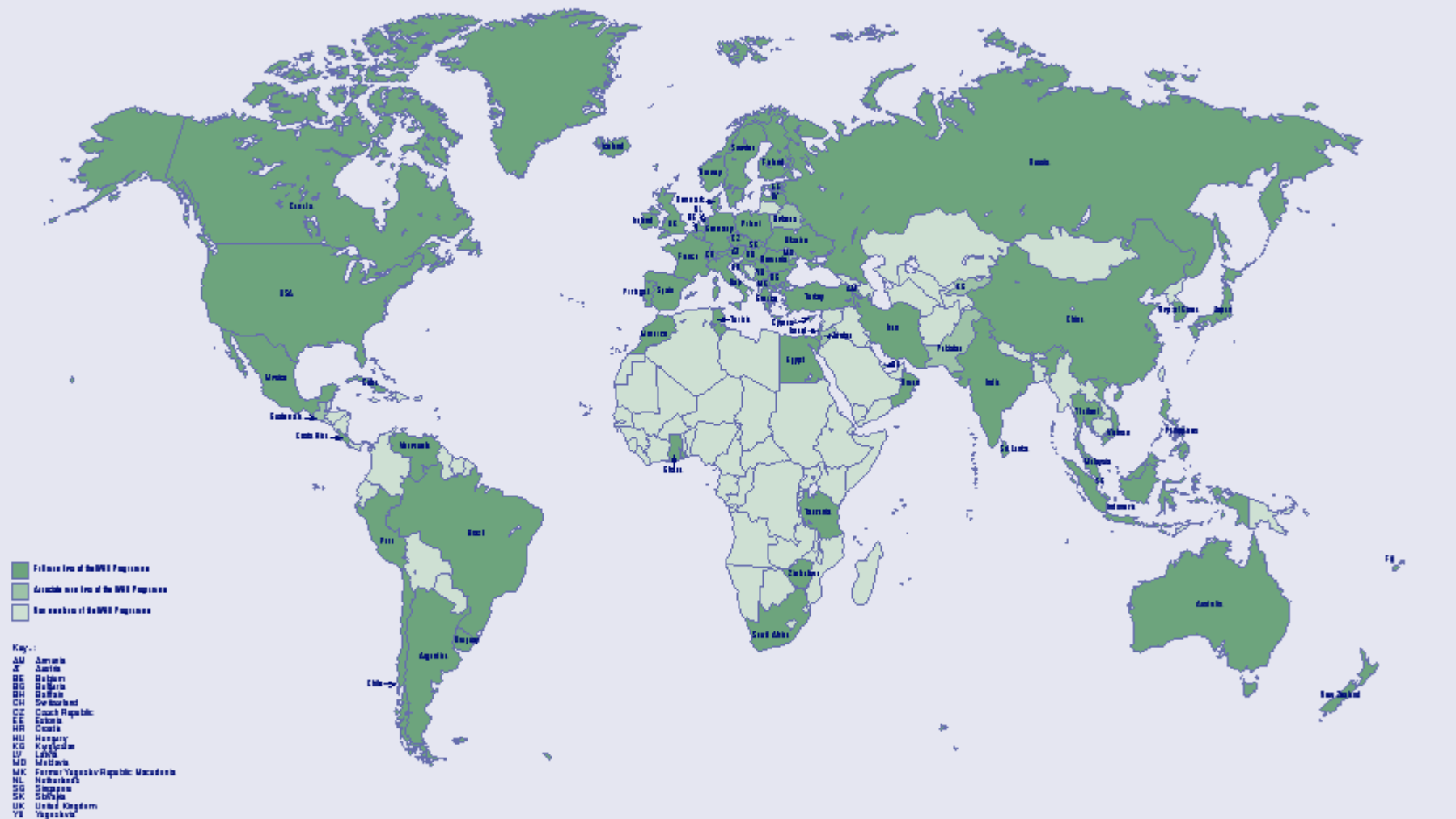


Aims of International Pharmacovigilance

- An early warning system through world-wide pooling of data
- Comparison of experiences between countries
- Expansion of pharmacovigilance around the world
 - Know how
 - Tools
- Clearinghouse function

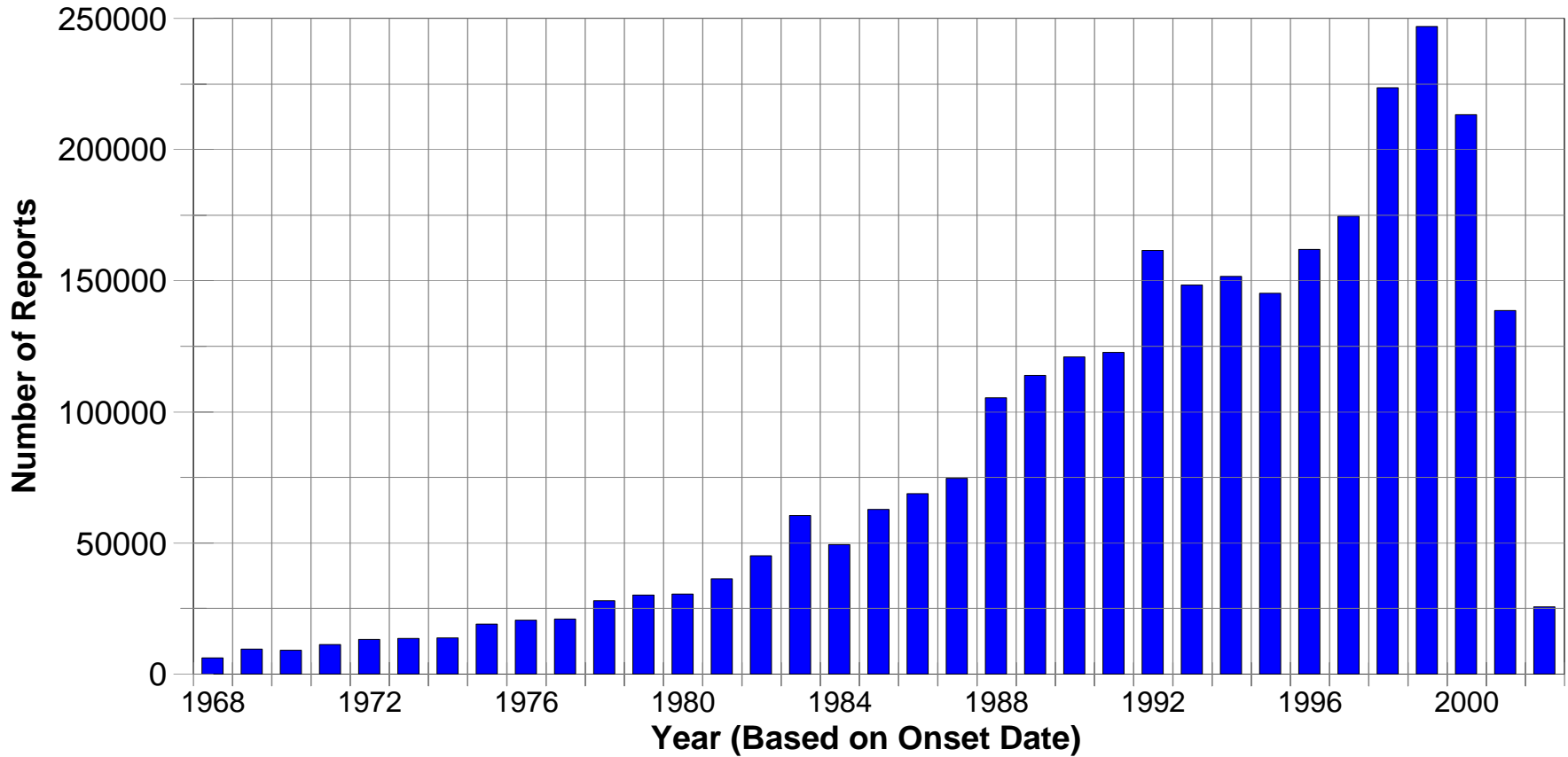


WHO Programme for International Drug Monitoring



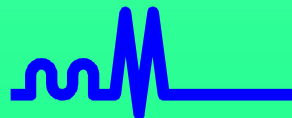
WHO Database 2002.07.27

Number of Reports by Year

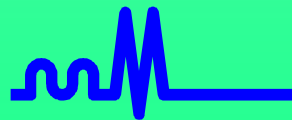
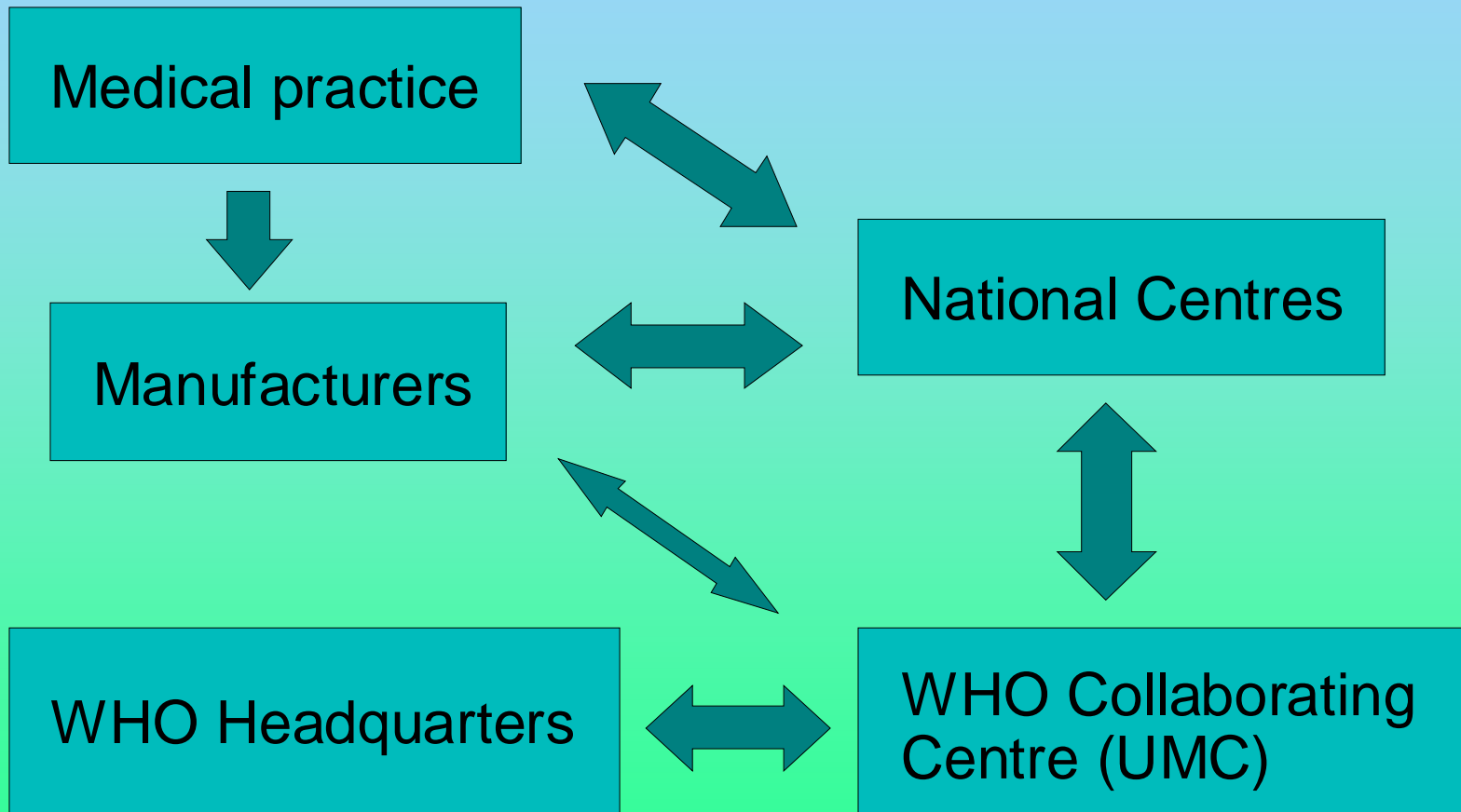


WHO Collaborating Centre *the* Uppsala Monitoring Centre

- Established as a foundation 1978
- Based on agreement Sweden - WHO
- International administrative board
- WHO Headquarters responsible for policy

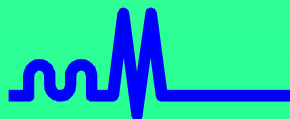


Flow of information



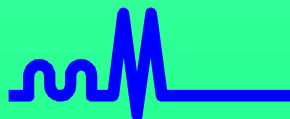
Submitting ADR Reports to UMC

- ICH - E2b format
- WHO agreed format



Functions 1

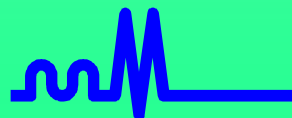
- Signal detection
 - Identification of previously unknown adverse reactions



Signal detection at the UMC

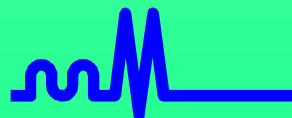
A combination of

- Automated quantitative data mining
- Human assessment
 - National Pharmacovigilance Centres
 - Review Panel
 - UMC staff



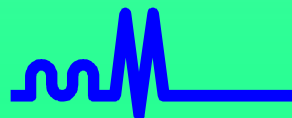
Why computerized quantitative data assessment?

- Enables management of very large amounts of data
- Automatic, no manpower/time
- Unexpected connections
- No "investigator's bias"



Automated selection for further assessment of combinations that stand out quantitatively against the background, using a Bayesian confidence propagation neural network (BCPNN)

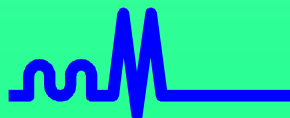
Eur J Clin Pharmacol 1998;54:315-321



The BCPNN network is used to count:

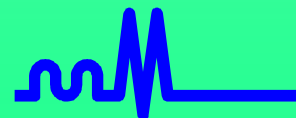
- All reports in the database
- All occurrences of variable x (e.g. ADR)
- All occurrences of variable y (e.g. drug)
- All occurrences of x and y together

Easily adapted to count occurrences of other variables

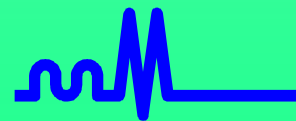
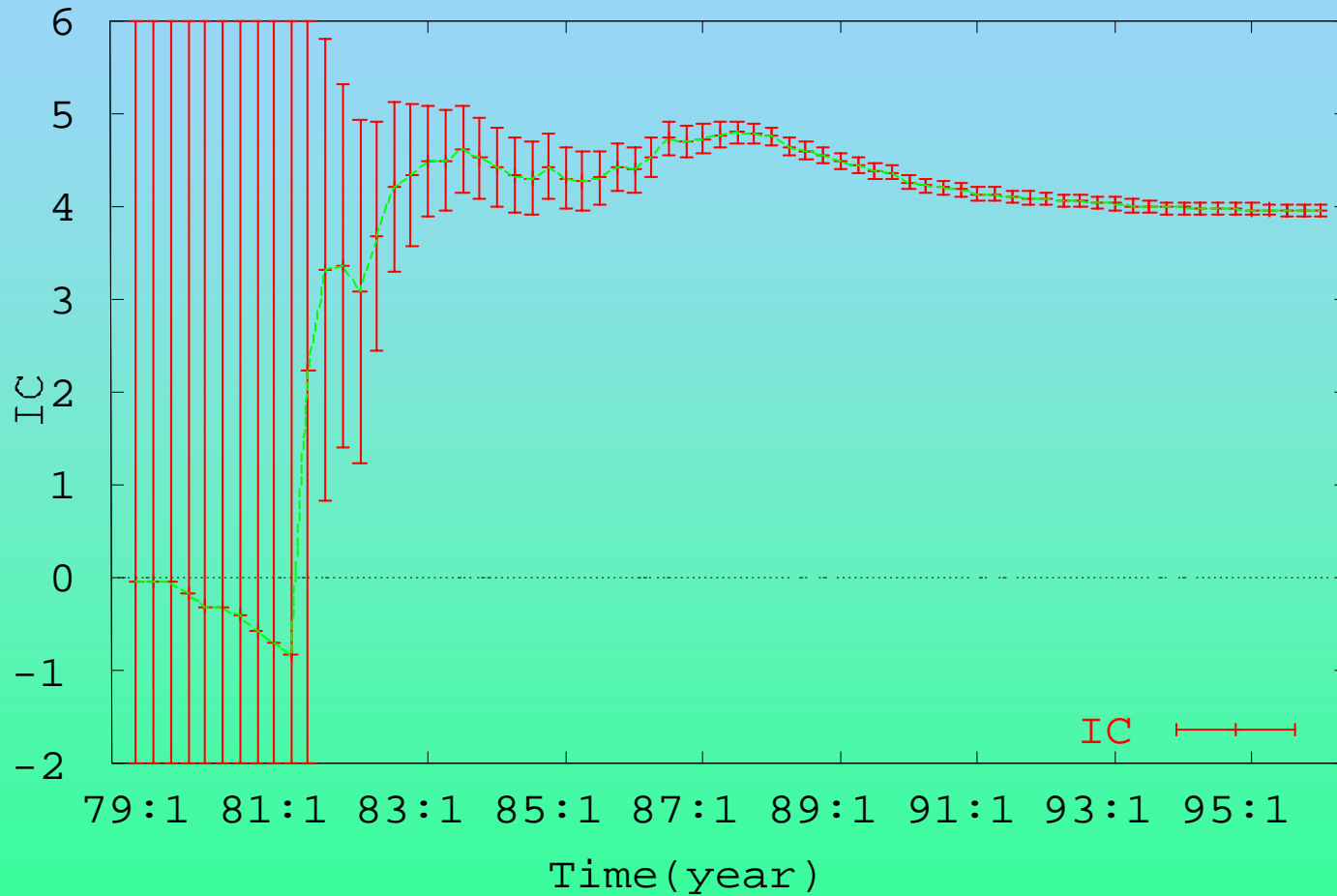


BCPNN Statistical Disproportionality

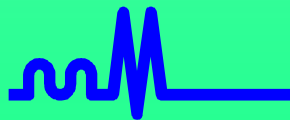
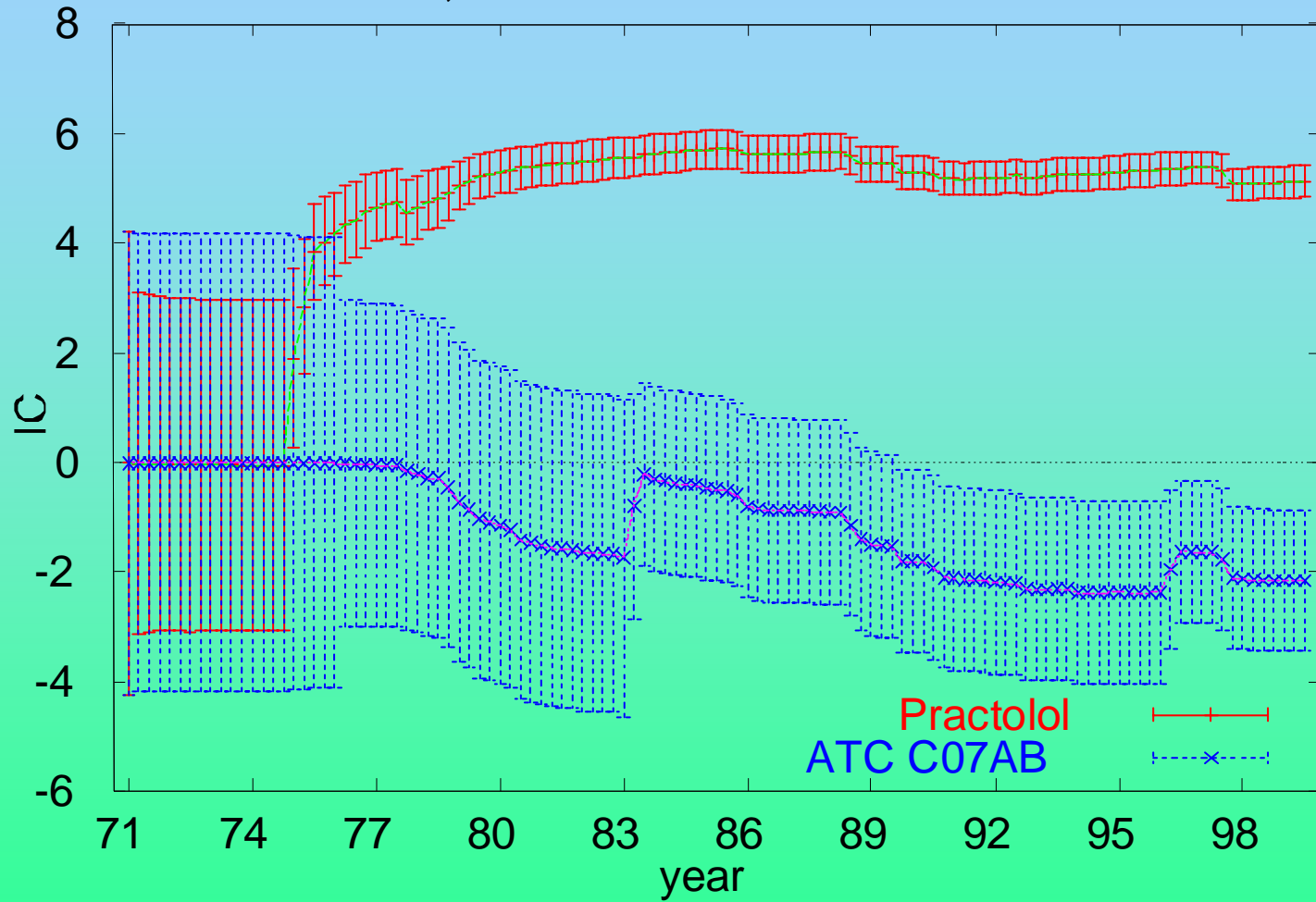
- IC Information Component: strength of the association between a drug and an ADR. Positive IC values indicate that the combination has been reported more often than expected from the generality of the database. The higher the IC, the more the combination stands out from the background (logarithmic scale).
- IC-2std: IC minus two standard deviations. This is the lower value of the 95% confidence interval.



Captopril - Coughing

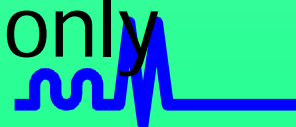


Practolol, ATC C07AB - Peritonitis



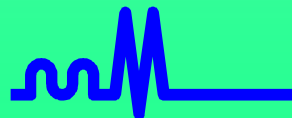
Combinations Database - combinations reported in the present quarter

- Drug name (WHO Drug Dictionary; ATC code)
- Adverse reaction term (WHOART; System Organ Class)
- Total no of reports of combination in database
- Total no of reports of drug (all ADRs)
- Total no of ADR (all drugs)
- No of reports of combination, present quarter only
- No of reports of drug (all ADRs), present quarter only
- No of ADR (all drugs), present quarter only



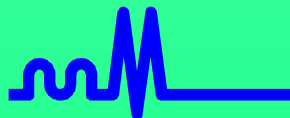
Combinations Database

- IC
- IC-2std
- Old IC (previous quarter)
- Old IC-2std (previous quarter)
- Year and quarter of first introduction
- Single / multiple ingredient drug
- Critical WHOART term?
- Dependence indicator?
- Documentation quality grading
- Positive rechallenge?
- Fatal outcome?
- Described in ADIS Reactions?



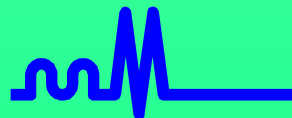
Associations Database

- Selection from the Combinations Database of all combinations with a positive IC-2std (having passed the threshold of the lower confidence interval value)

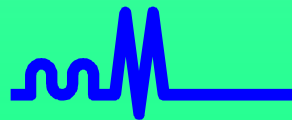
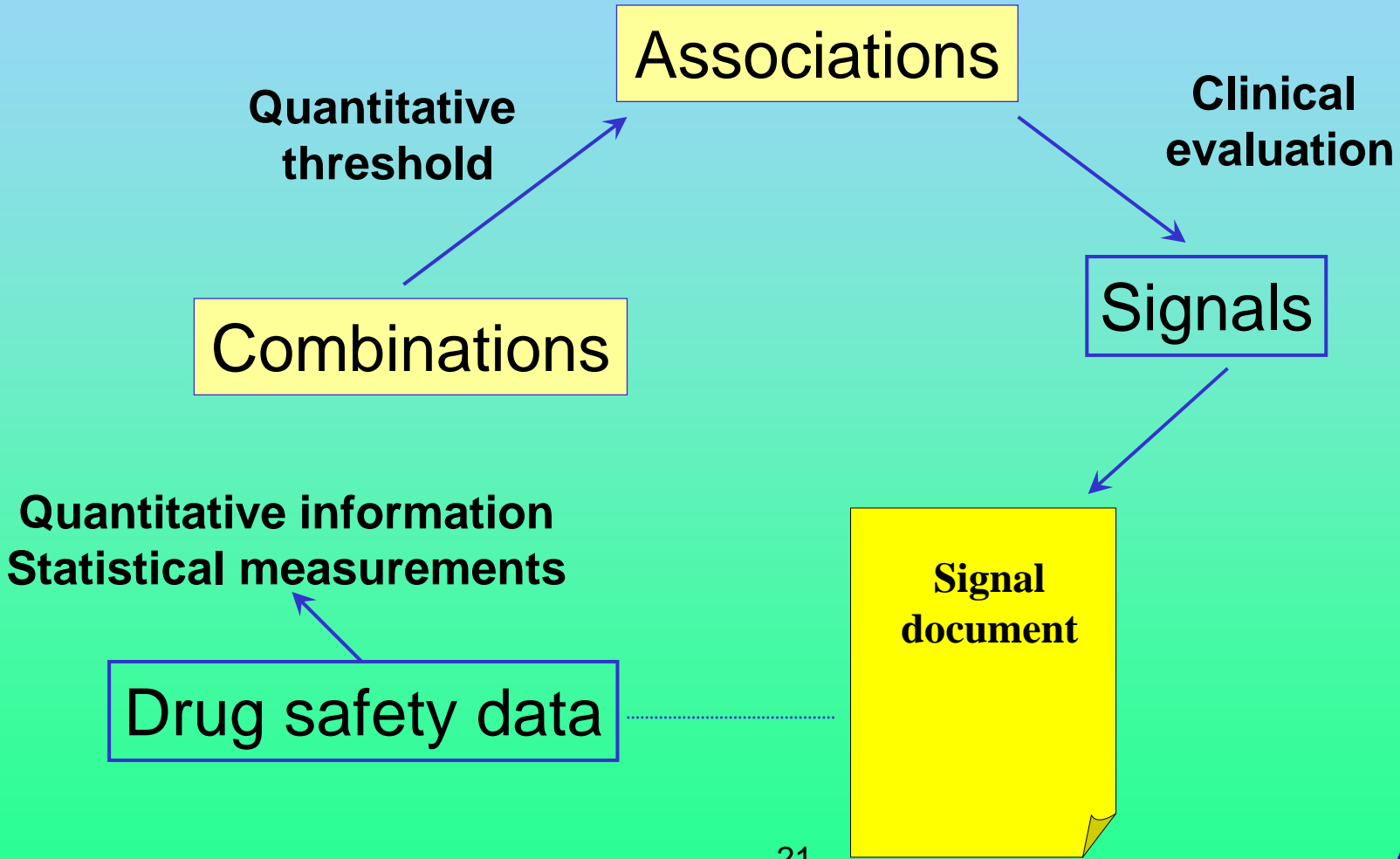


UMC Signal Review Panel

- 35 expert reviewers in 21 countries
- Evaluation of System Organ Classes, ATC groups and special interests
- Clinical and pharmacological assessment
- Case evaluations
- Findings presented in SIGNAL document



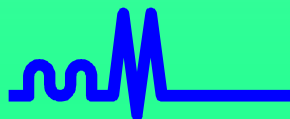
Procedure for signal analysis



New Signalling Procedure

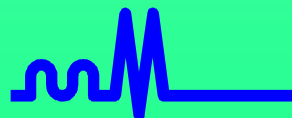
What should be achieved?

- Signals should not be missed
- Signals should be found early
- 'False' signals should be kept to a minimum



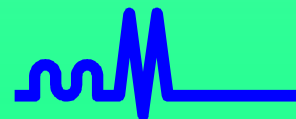
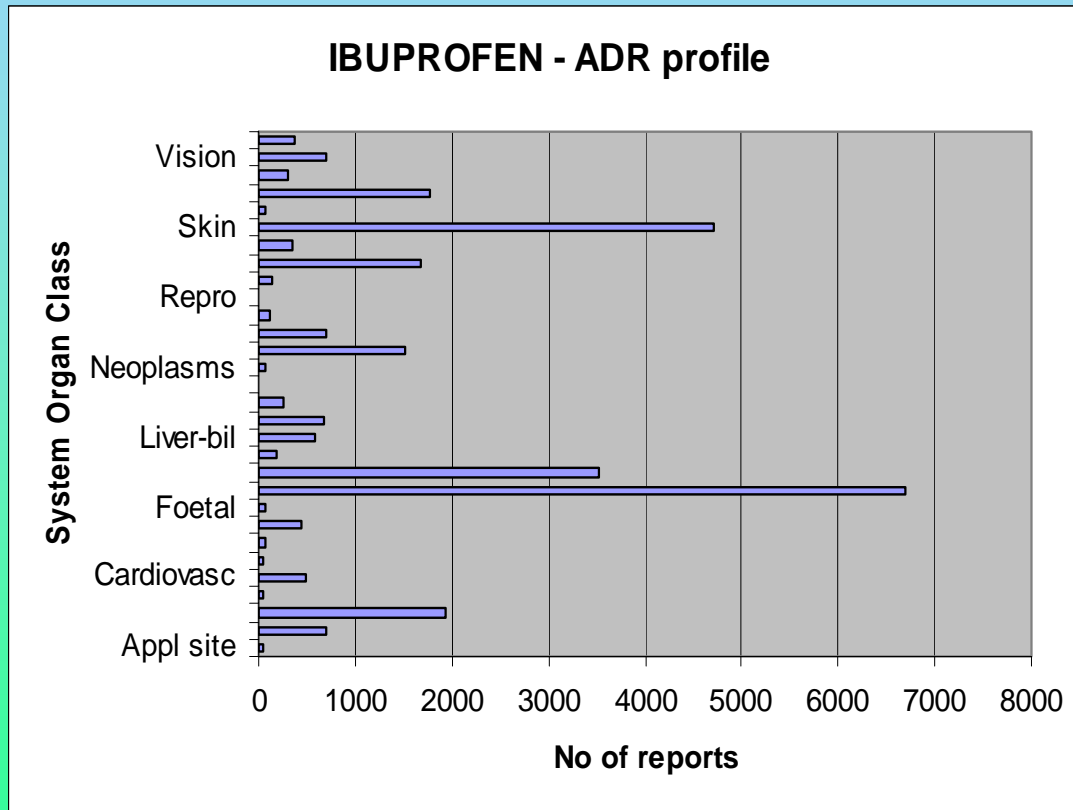
Functions 2

- Signal strengthening
 - Annual 'Type-A' document
 - Search requests
 - Web-based search programme
 - Collaboration (e.g. Drug Surveillance Research Unit, Southampton)



Functions 3

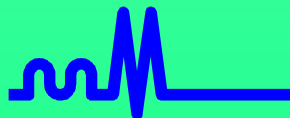
- Adverse reaction profiles



Functions 4

Comparing national experiences

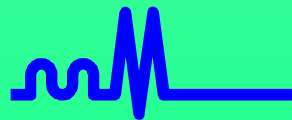
- A suspicion may be strengthened if similar observations are made in many countries
- If an association is reported in only one country there may be a country-specific problem



International Differences

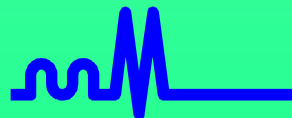
Real or Apparent?

- Clioquinol SMON
- metamizole agranulocytosis
- mianserin agranulocytosis
- nitrofurantoin pulmonary;
neurological
- oestrogens jaundice
- triazolam psychosis
- acetylsalicylic acid Reye's syndrom
- flucloxacillin hepatitis



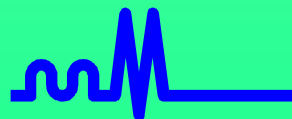
International Differences (Quantitative and Qualitative)

- Disease prevalence
- Genetic, social, cultural, traditional
- Foods, herbals, alcohol, other drugs
- Healthcare systems
- Health professional practices
- Indication for, and use of medicines
- Pharmaceutical formulations
- Drug monitoring practices



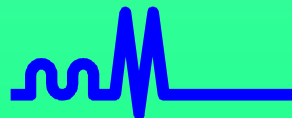
Functions 5

- Identification of risk factors



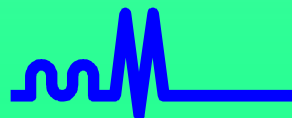
Possible Risk Factors

- Users population, indication
- Other medicines
- Genetic constitution
- Dosage
- Duration of treatment
- Route of administration
- Availability ('over the counter')
- Warnings and instructions for use
-



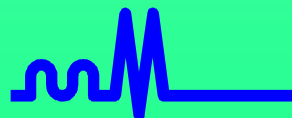
Functions 6

- Combining ADR figures with other data
 - drug utilization statistics (IMS)
 - population statistics



UMC - a communication centre

- WHO Pharmaceuticals Newsletter
- Uppsala Reports
- Internet home page
 - <http://www.who-umc.org>
- Vigimed e-mail discussion group



WHO PHARMACEUTICALS NEWSLETTER

prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Stockholm, Sweden

No. 1, 2001

The new WHO Newsletter is a biannual publication in the English language for pharmaceutical products, based on information received from regulatory authorities in WHO member states. It is published in both print and electronic versions. The print version is published biannually in February and August, and the electronic version is published quarterly in February, April, June and August. The electronic version is available in HTML and PDF formats. It is available in both print and electronic versions.

Dr. John Hensler and Lynn
MARRAS, WHO WHO
World Health Organization
250 Avenue P, International
E-mail address: JHensler@who.int
Page: 44/27/01/01/01

For more information on WHO's role in
international drug monitoring,
please visit our website at:
www.who.int/medicines

For more information on WHO's activities,
please visit our website at:
www.who.int
WHO Collaborating Centre for
International Drug Monitoring
Stockholm, Sweden
Tel: +46 (0) 8 33 88 00 Fax: +46 (0) 8 33 88 01
E-mail: icdm@icdm.se
Internet: www.icdm.se

Contents ■

- Regulatory matters ■
- Safety of Medicines ■
- Medication errors ■
- Feature: MMR vaccine ■

EDITORIAL

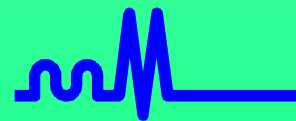
In this first issue for 2001, we include an article by the staff of the Vaccines Programme in WHO on the triple vaccination — measles, mumps and rubella (MMR). The text provides a summary of the WHO position on the vaccine. This is a significant departure from the well-defined role of WHO to facilitate the exchange of information. In the last editorial we used it was not WHO's task to issue statements on decisions taken by competent regulatory authorities. However, we should like to hear from you on this controversial issue. Is it correct for WHO to make statements on drugs or do you think we should continue simply providing a forum for exchange of information? Please do let us know. We eagerly await your input to our Newsletter.

The Council for International Organizations of Medical Sciences (CIOMS) has convened another group, CIOMS VI, to continue preparation of their series of safety information on drugs. This group is looking into the safety of drugs during clinical trials. WHO and the Uppsala Monitoring Centre are once again pleased to be members of this group where regulators and the pharmaceutical industry can meet amicably. The first meeting took place in Geneva earlier this month and one of the important discussion points was whether the term "pharmacovigilance" extends to pre-authorization as well as post-authorization of drugs.

Please note also the first announcement for the 24th Annual Meeting of National Centres participating in the WHO Programme on International Drug Monitoring. We shall keep you informed of progress.

Useful Internet addresses:

The Therapeutic Goods Administration in Australia has created a Webpage on prescribing medicines in pregnancy:
<http://www.health.gov.au/8996arbcu/html/psiprescribing.htm>
The US Pharmacopoeia webpage includes information and links on veterinary medicines as well as human medicines including medication errors (see p. 7):
<http://www.usp.org/>



Issue 17
January 2002

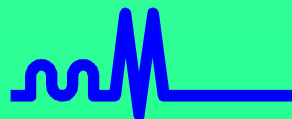
Published by the
Uppsala Monitoring
Centre, 2002

Uppsala **REPORTS**

For everyone concerned with the issues of pharmacovigilance and toxicovigilance

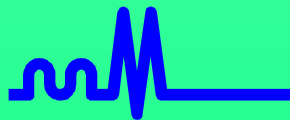


- Successful Annual Meeting in Dunedin page 3
- Reports from Asia-Pacific Region pages 4-7
- New Signal Detection Strategy pages 8 and 9
- New major publication from the UMC page 10



Training and technical support

- Training courses
- Regional and local activities
- Internet-based training
- Documentation of established systems



COUNTRY PROFILES
AND OVERVIEW

EDITED BY
STEN OLS

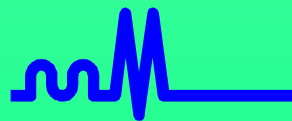
NATIONAL

PHARMACOVIGILANCE

SYSTEMS

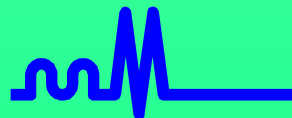


WHO Collaborating Centre for International Drug Monitoring



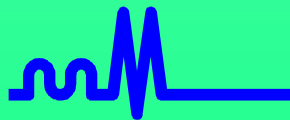
UMC involvement in local activities, 1998 - 2002

- 1998 - Norway, China, Portugal, Malaysia, Morocco, India
- 1999 - Philippines, Venezuela, Mexico, South Africa
- 2000 - India, China, Kuwait, Romania, Uruguay
- 2001 - Oman, Russia, Ghana, Fiji, Singapore, Vietnam
- 2002 - Cuba, Chile, Morocco



Technical support

- Guidelines
- Terminologies
- Software development
- Literature coverage





AIDE MEMOIRE

For a national strategy for safe drugs and their appropriate use.

During last decades it has been demonstrated that medicine related morbidity and mortality is one of the major health problems.

It has been estimated that adverse drug reactions are the 4th to 6th largest cause for mortality in some countries. The percentage of hospital admissions due to such reactions is 10-20%. There is a concomitant high economic impact on health care services. Some countries spend up to 15-20% of their healthcare budget on drug-related problems.

Medicine induced morbidity and mortality can be substantially reduced through an integrated strategy for drug safety monitoring which includes:

- ❖ Establishment of the national pharmacovigilance service.
- ❖ Education and training of health care professionals on benefit/risk assessment and rational use of drugs.
- ❖ Behaviour change amongst patients and healthcare workers to decrease unnecessary and irrational use of drugs.

A well organized drug safety management - pharmacovigilance service is a prerequisite for the early detection of the risks of drugs, prevention of adverse drug reactions (ADR) and aiding health professionals and patients to make the best benefit/risk assessment for safe and effective pharmacotherapy.

Pharmacovigilance plays a major role in pharmacotherapy decision-making, be it individual, regional, national or international.

Words of advice

- ❖ **Secure government commitment and support for the national pharmacovigilance programme.**
- ❖ **Establish a National Centre for Pharmacovigilance as a separate unit with responsibility and authority, an adequate budget and trained staff.**
- ❖ **Develop a national policy and action plan.**
- ❖ **Provide information on drug safety to healthcare professionals and consumers.**
- ❖ **Educate and train healthcare providers on rational use of drugs and pharmacotherapy monitoring.**
- ❖ **Monitor the impact of activities on the safety of pharmacotherapy.**

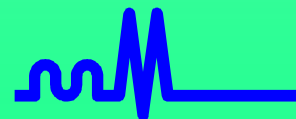
Checklist

Pharmacovigilance service

- Government commitment and support
- Legislation/regulation
- National pharmacovigilance policy/plan
- National Pharmacovigilance Centre with responsibility and authority
- Adequate resources for pharmacovigilance activities
- National system of drug registration and quality control
- National system of postmarketing surveillance including requirements for pharmaceutical companies in relation to continuous benefit/risk assessment and periodic safety update reporting

National policy on the safe and appropriate (rational) use of drugs

- Undergraduate and continuing education on rational use of drugs
- Assessment of pharmacotherapy practices
- Promotion of rational use of drugs
- Preparing and distribution of educational and informational materials
- Monitoring and evaluation of activities

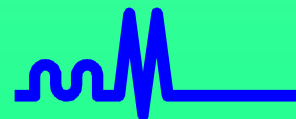




Organización Mundial de la Salud

VIGILANCIA DE LA SEGURIDAD *de los* **MEDICAMENTOS**

Guía para la instalación y puesta en
funcionamiento de un Centro de Farmacovigilancia

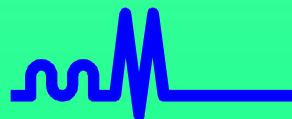


The
IMPORTANCE
of **PHARMACOVIGILANCE**

Safety Monitoring of medicinal products

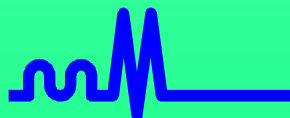


World Health
Organization
2002



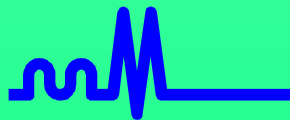
UMC Functions

- Harmonisation



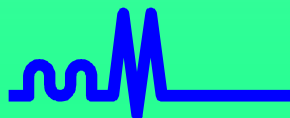
Terminologies

- WHO Adverse Reaction Terminology
- WHO Drug Dictionary
- ATC Classification
- ICD Classification



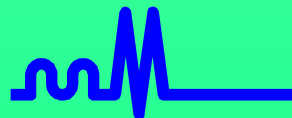
Definitions established within the WHO Programme

- Adverse reaction
- Adverse event
- Side effect
- Signal
- Serious reaction
- Causality categories



Worldwide network of knowledge and competence

- Bilateral contacts facilitated
- Annual meeting of representatives of National Centres
- Collaboration with academia (e.g. Utrecht University)
- Working relations with relevant organizations - *CIOMS, ISoP, ISPE, DIA, IPCS, HAI, IFPMA, etc*



Drug Safety™

Reprint Collection 2001
ISSN: 0144-9916

PHARMACOVIGILANCE IN FOCUS

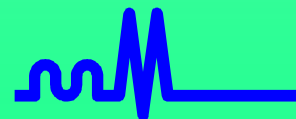
A Selection of Articles Concerning the Theory and Practice of Pharmacovigilance

with contributions by

I. RALPH EDWARDS
MARIE LINDQUIST
RONALD MEYBOOM
STEN OLSSON

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Reactions™

weekly

Validating the Adverse Reaction News for Your The UPSALA Monitoring Centre

ISSN 1365-2330

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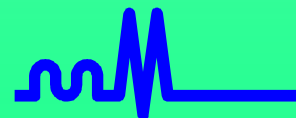
HIGHLIGHTS

- Statins: risk of fatal rhabdomyolysis** 2
- MMR vaccine: no evidence for new autism variant** 3

| | | | |
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| Amidostyline/splenectomy | 2 | Clarithromycin: interaction with concomitant antibiotics leading to ergotism (✱✱) | 8 |
| Statins: risk of fatal rhabdomyolysis | 2 | Clonidine: ovarian hyperandrogenism syndrome (✱) | 7 |
| Pharmacoepidemiology & Regulatory News | | Crucifer: type 2 diabetes mellitus | 8 |
| Drospirenone: cardiovascular warnings issued by Health Canada | 3 | Cyclosporin: interaction with concomitant antibiotics leading to an increased serum cyclosporin concentration (✱) | 8 |
| Herbal medicine: Health Canada issues "Stay fit" warning | 3 | Dexamethasone/steroidosteroids: femoral head necrosis (✱) | 8 |
| Adverse Reaction Research | | Etiology/epidemiology: angioneurotic edema | 7 |
| Alzheimer's disease vaccine trial halted due to CNS inflammation | 3 | Ergotamine: interaction with concomitant diazepam leading to ergotism (✱✱) | 8 |
| Antidotes/risks: risk of early fetal death | 3 | Ethyllostradiol: occlusive colitis | 8 |
| Epilepsy: associated with HIV dementia and depression | 4 | Fingolimod: acute myeloid leukaemia (✱) | 8 |
| Epinephrine: oral self-applied and antihypertensive antibiotics | 5 | Fluoxetine: interaction with concomitant mefenamic acid/acetaminophen (✱) | 10 |
| MMR vaccine: no evidence for new variant of autism | 2 | Gabapentin: absence seizures | 9 |
| Paclitaxel-induced liver failure: lactate levels predict mortality | 4 | Clozapine: interaction with concomitant carbamazepine leading to thibolone/olanzapine (✱✱) | 7 |
| Permethrin: CNS excitation at high dosages | 5 | Risperidone: delayed-onset thrombocytopenia and thrombosis (✱) | 9 |
| Rifampin: no increased risk of exercise-induced myocardial ischaemia | 4 | Sildenafil/sildenafil/vasodilators: fatal pulmonary arterial hypertension (✱) | 6 |
| TRT: increased risk of breast cancer | 5 | Infliximab: paraneoplastic pemphigus (✱✱) | 9 |
| Adverse Reaction Case Reports | | Intermittent pulmonary alveolar proteinosis (✱✱) | 9 |
| 5-methoxypsoralen: ataxiparisis (✱✱) | 8 | Levofloxacin: acute hepatocellular injury | 9 |
| ADON-L: hypertension and tachycardia (✱) | 8 | Lyme disease vaccine: arthritis (✱) | 9 |
| Amisulpride/olanzapine/risperidone: femoral head necrosis (✱) | 8 | Mefenamic acid: acute lung injury (✱) | 10 |
| Amisulpride/risperidone/sildenafil: fatal pulmonary arterial hypertension (✱) | 8 | Mefenamic acid: chronic diarrhoea | 10 |
| Amiflopryzole: pleurisy, sinus bradycardia and respiratory distress (✱) | 7 | Mirtazapine: interaction with concomitant Bupropion leading to an increased serum mirtazapine concentration (✱) | 10 |
| Artemether: interaction with concomitant cyclosporin leading to an increased serum cyclosporin concentration (✱) | 8 | Obeticholic acid: hyperglycaemia and ketonuria (✱) | 10 |
| Bupropion: urinary and faecal incontinence | 7 | Ondansetron: ataxiparisis (✱) | 11 |
| Caproic acid/salicylic acid/salicylic acidemia | 7 | Optimast/propofol: ventricular tachycardia | 11 |
| Carbamazepine/salicylic acid/salicylic acidemia | 7 | Propofol/propofol: ventricular tachycardia | 11 |
| Cervarix: interaction with concomitant gabapentin leading to thibolone/olanzapine (✱✱) | 7 | Propylthiouracil: Chang-Ming syndrome (✱✱) | 11 |
| | | Roacutane: fatal liver failure (✱) | 11 |
| | | Sertraline: pancytopenia (✱) | 11 |
| | | Valerian: gingivitis (✱) | 12 |

the UPSALA
MONITORING
CENTRE

adis
INTERNATIONAL
2 Parkside Square, London



WHO/EDM/QSM/2002.2
Original: English

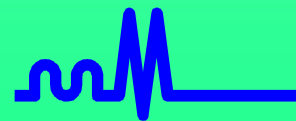
Safety of Medicines

A guide to detecting and reporting
adverse drug reactions

Why health professionals need to take action

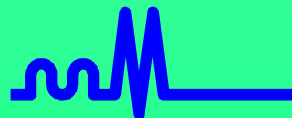


World Health Organization
Geneva 2002



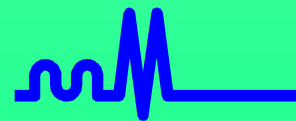
Research and development

- Methods for signal identification and analysis; complex connections
- Improved monitoring of herbal or traditional medicines
 - collaboration with Royal Botanical Gardens, Kew, UK
- Good communications practice in pharmacovigilance; collaboration with:
 - University of Verona
 - CIOMS



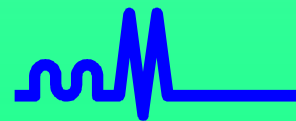
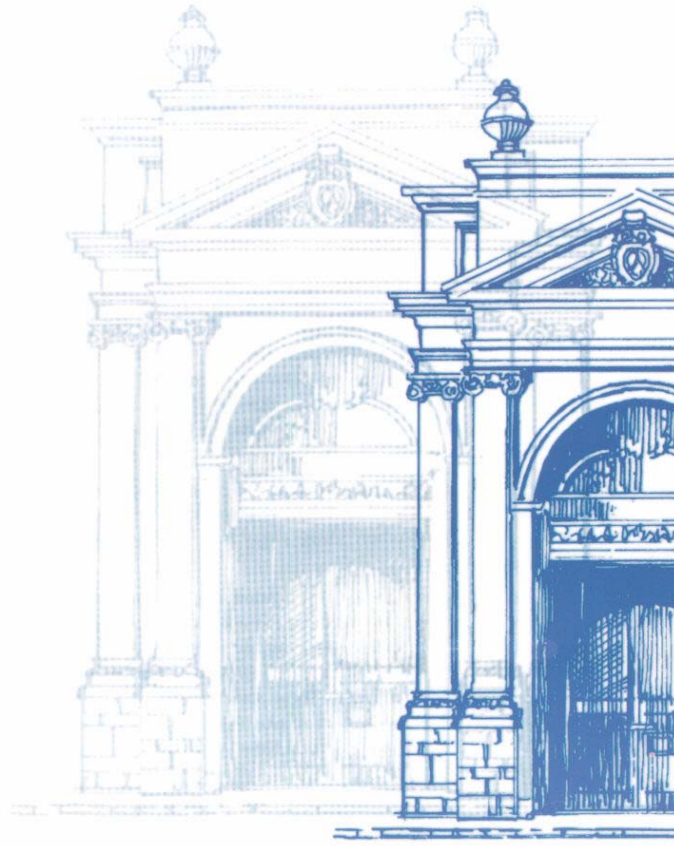
EFFECTIVE COMMUNICATIONS IN PHARMACOVIGILANCE

THE ERICE REPORT



DIALOGUE IN
PHARMACOVIGILANCE

more effective communication



Viewpoint

Watching for safer medicines

Part 1

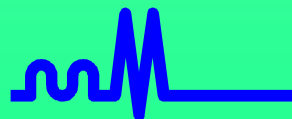
Issues, controversies and science in the search for safer and more rational use of medicines

 **the UPPSALA
MONITORING
CENTRE**



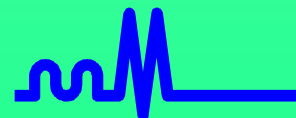
WHO Collaborating Centre for
International Drug Monitoring

An account of the WHO Programme for International Drug Monitoring, the work of the Uppsala Monitoring Centre and the challenges of worldwide collaboration for improved patient care and public health.



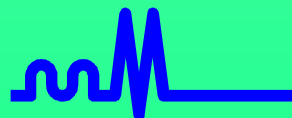
Drugs & problems of current interest

- Herbals monitoring programme
- Biopharmaceuticals
- Counterfeit products
- Vaccine vigilance
- Haemovigilance
- Safety of self-medication



Herbal-specific classification issues

- Heterogenous group
- "Substance" nomenclature
 - Genus + species + author
 - Parts and Extracts
- Botanical and vernacular synonyms
- Anatomical, therapeutical, pharmacognostic classification

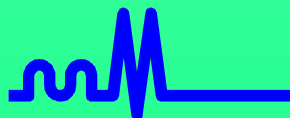


Herbal ATC classification

Eg. Herbal remedies for treatment of peptic ulcer A02W

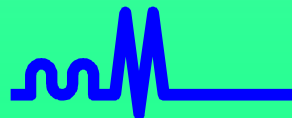
A02WA (containing saponins)

A02WB (containing mucilage)

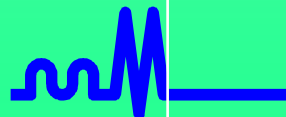
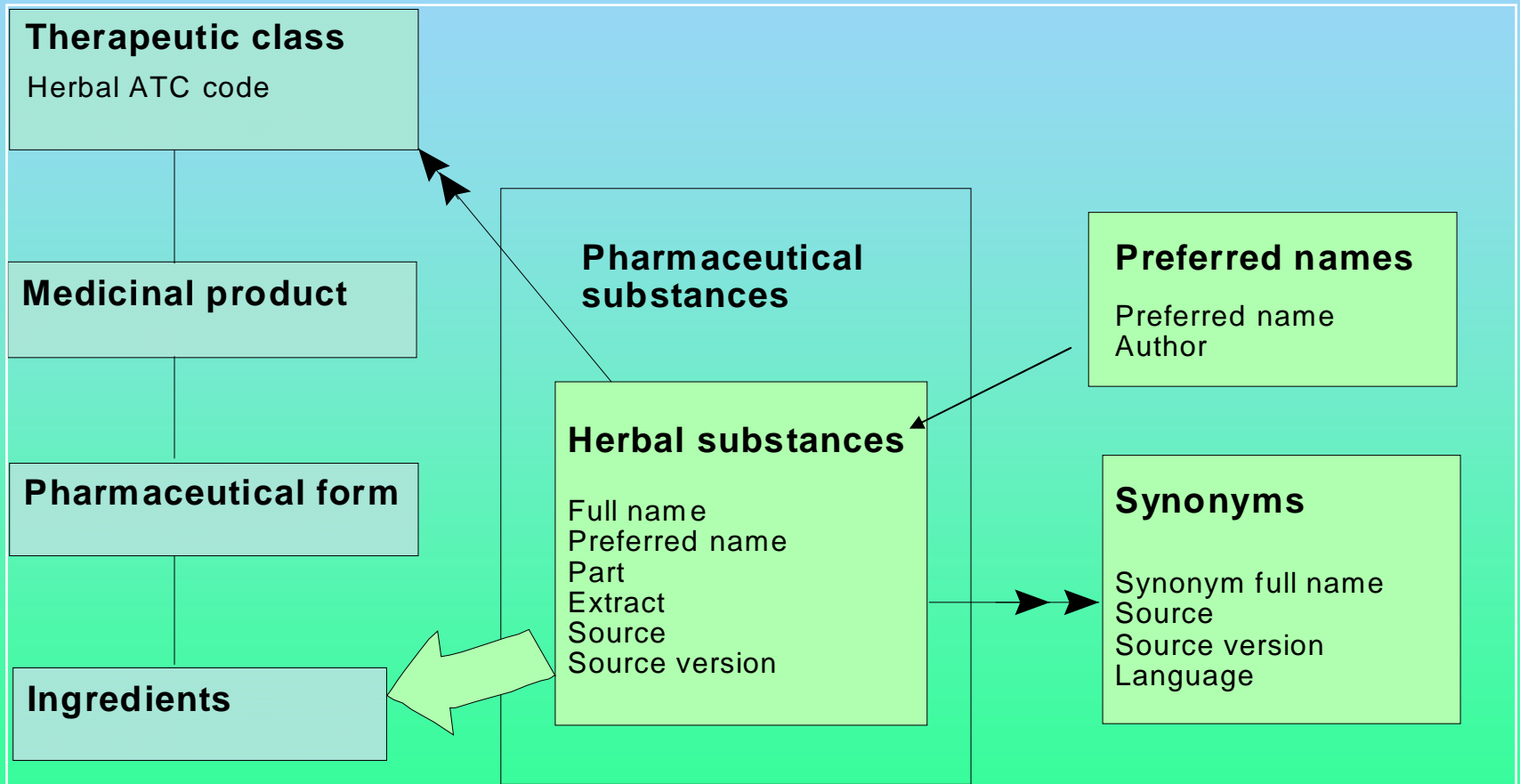


Improved herbals vigilance

- **Structured herbal substance register**
 - Retrieval of related reports
 - BCPNN calculations
- **Herbal ATC classification**
 - Selective herbal searches
 - Retrieval of summary data
 - Group comparison searches
- **Synonym check list**



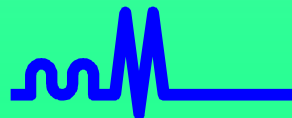
Herbal info in Drug Dictionary



WHO Data Base on Counterfeit Pharmaceuticals (K. Kimura, Geneva, 1998)

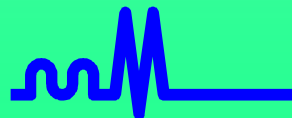
- **751 Cases of counterfeiting (1982-1997)**
 - **25% developed countries**
 - **65% developing countries**
- **Majority discovered by visual detection**
- **All classes of drugs - predomination of antibiotics**

WHO Guidelines for the development of measures to combat counterfeit drugs



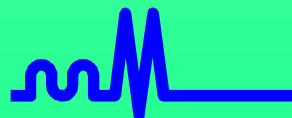
WHO Guidelines for the development of measures to combat counterfeit drugs

- http://www.who.int/medicines/organization/qsm/activities/qualityassurance/counterfeit/counterfeit_info.shtml



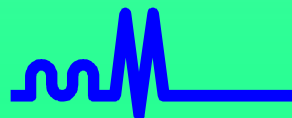
Data available to non-members

- On request to WHO Uppsala Monitoring Centre
- Consent from participating countries (automatic from 49 countries)
- Quantitative listings
- Caveat Document

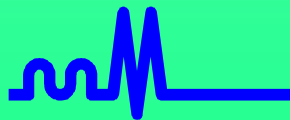


Ideas in Planning Phase

- Single international database for industry reports
- Phenotype/genotype testing of patients experiencing adverse events
- Chemical structure/clinical safety relationship



Thank you for your attention



Definitions WHO

Edwards IR, Biriell C. Drug Safety 1994;10:93-102

- Side Effect: Any unintended effect of a drug occurring at normal doses, which is related to the pharmacological properties of the drug.
- Adverse Event: Any untoward medical occurrence that may present during treatment with a drug but does not necessarily has a causal relationship.
- Adverse Reaction: Any response to a drug that is noxious and unintended and occurs at normal doses

