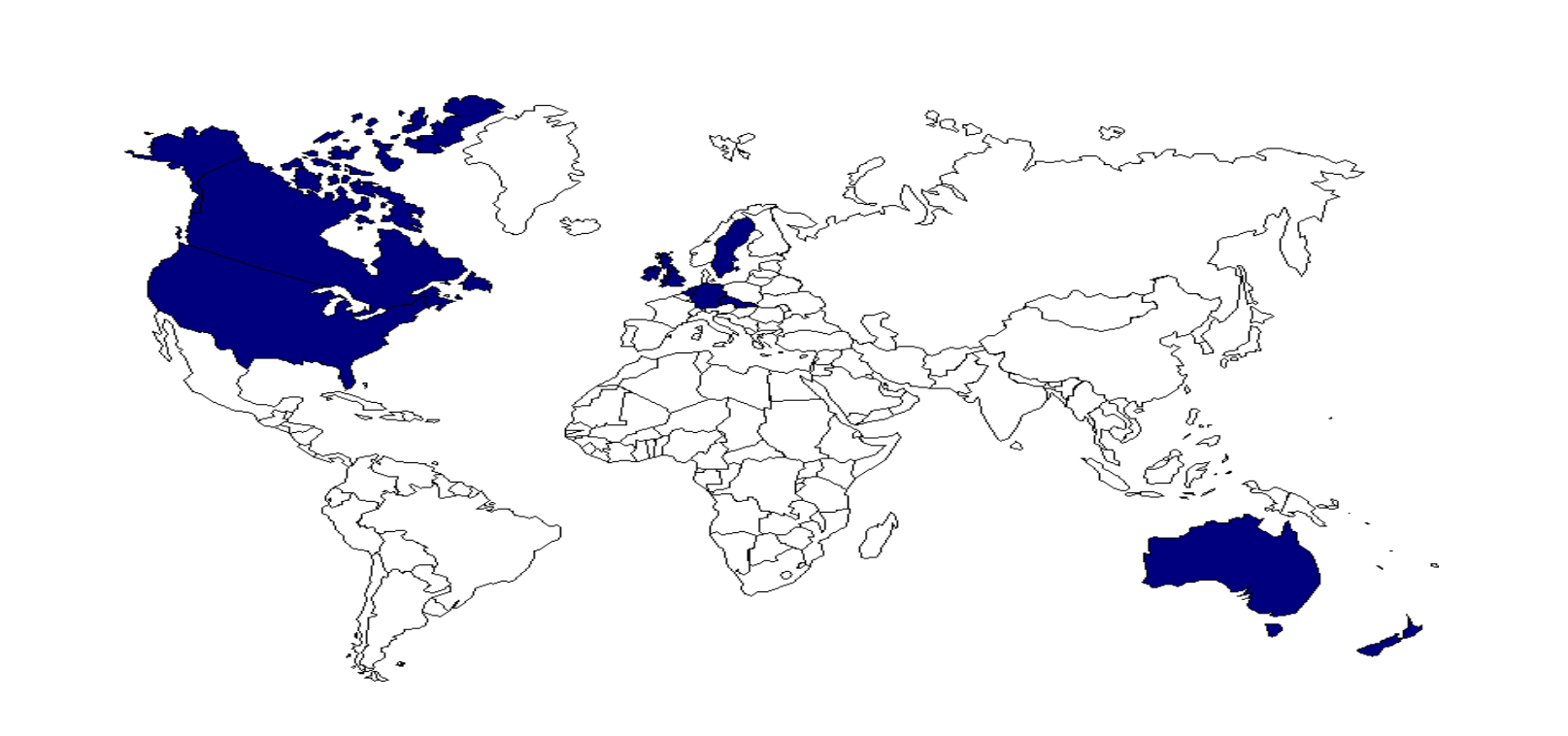
WHO Collaborating Centre for International Drug Monitoring

the Uppsala Monitoring Centre

www.who-umc.org

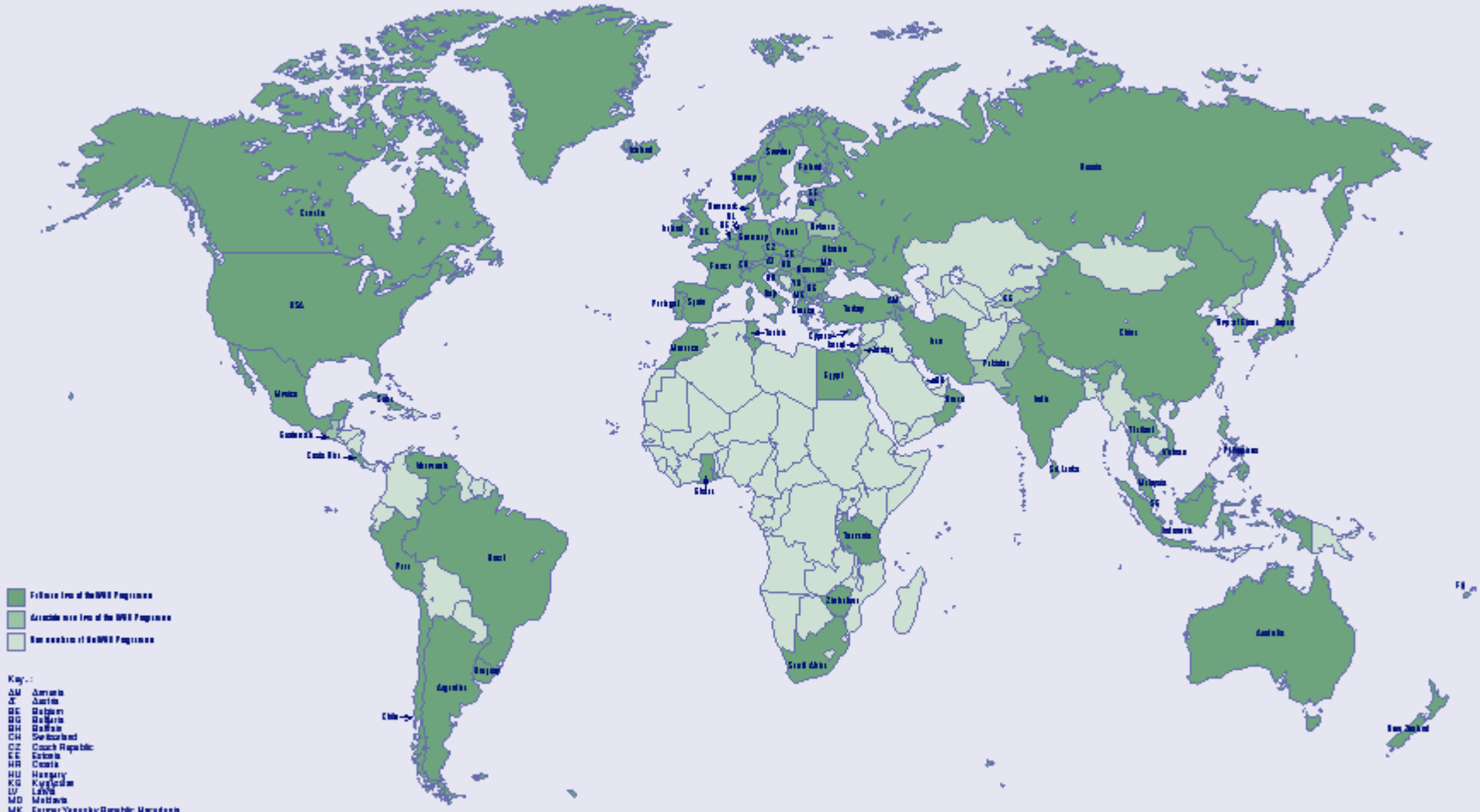
WHO Drug Monitoring Programme
Founding Members 1968



Aims of International Pharmacovigilance

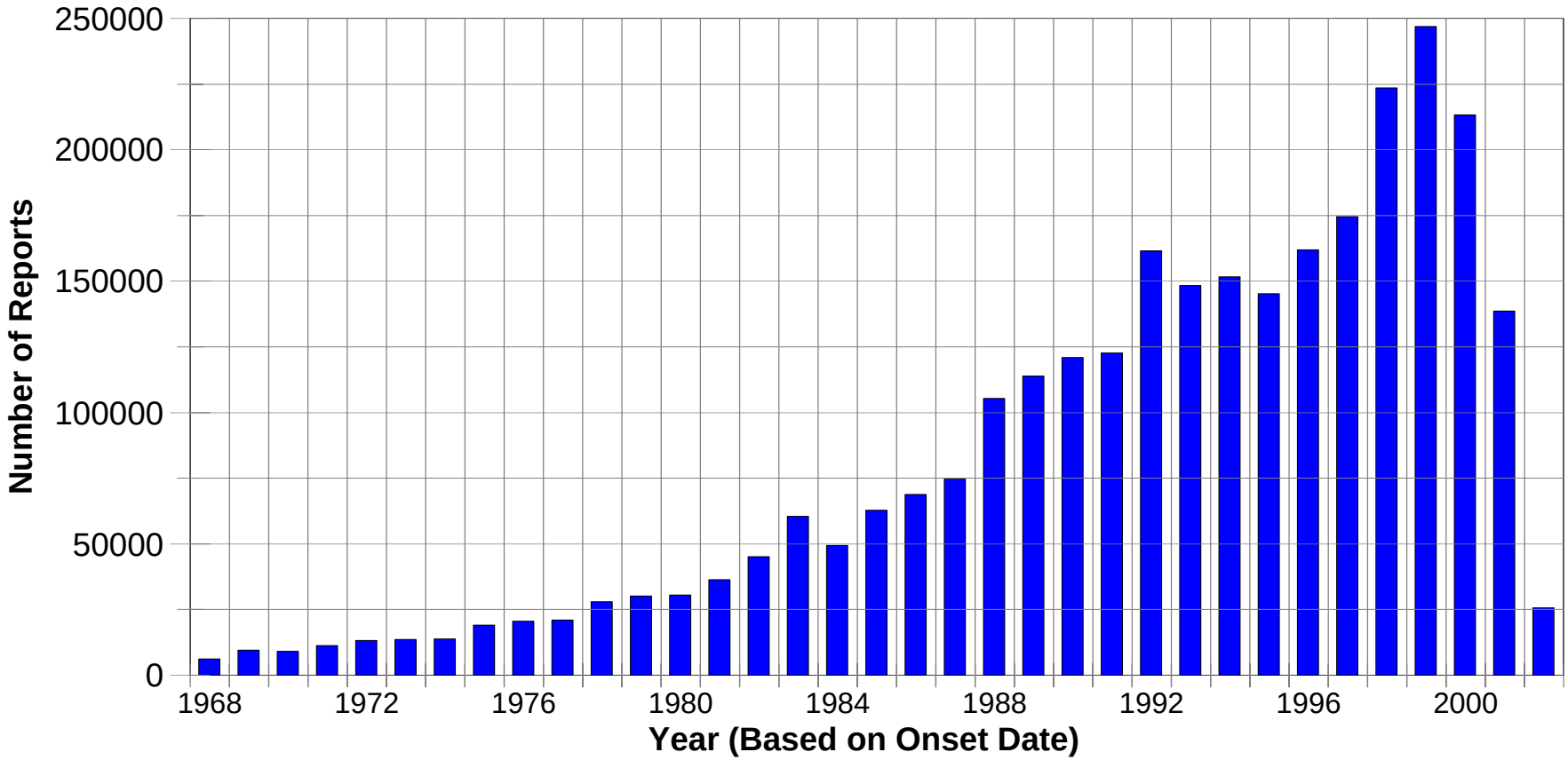
- An early warning system through world-wide pooling of data
- Comparison of experiences between countries
- Expansion of pharmacovigilance around the world
  - Know how
  - Tools
- Clearinghouse function

WHO Programme for International Drug Monitoring



WHO Database 2002.07.27

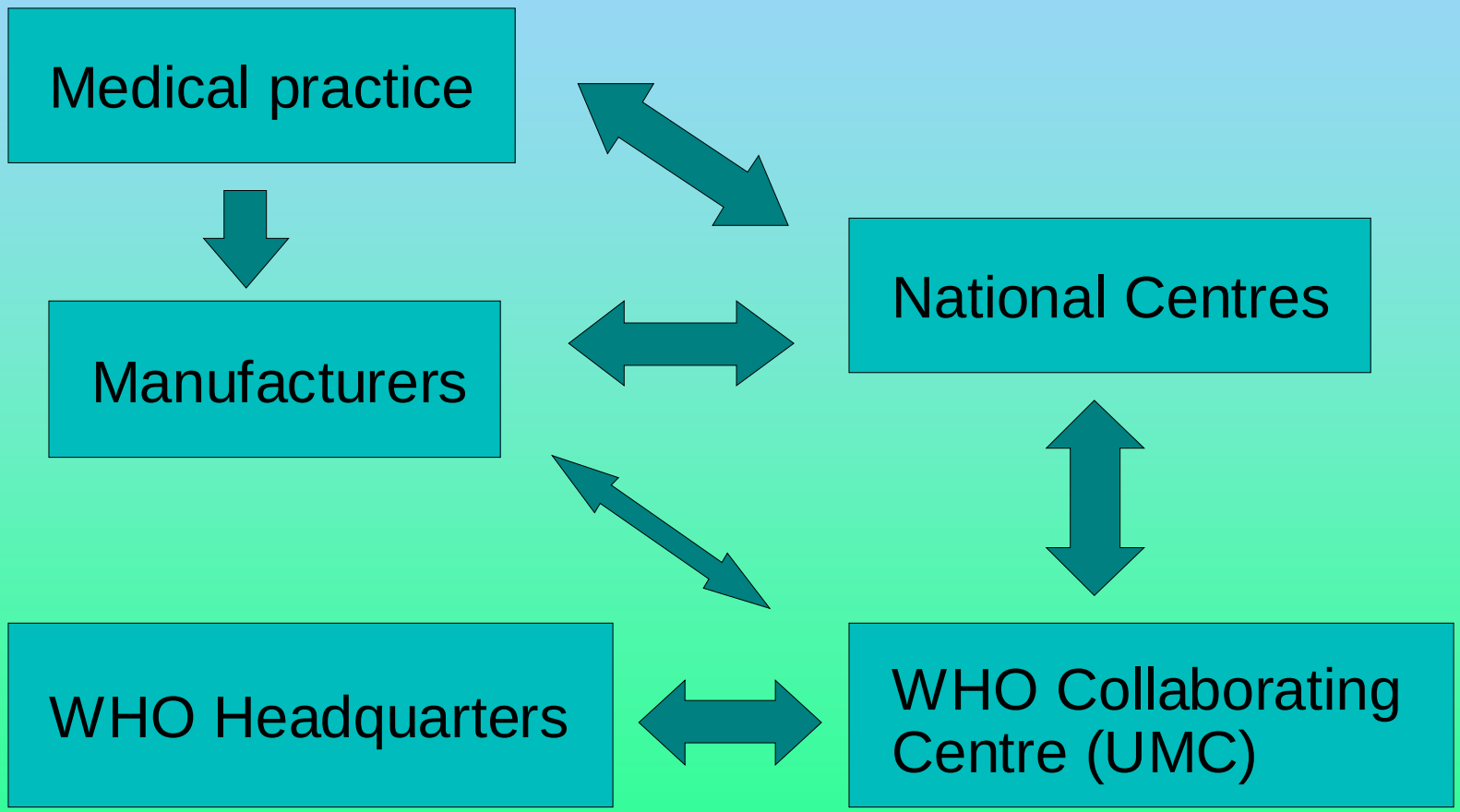
Number of Reports by Year



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

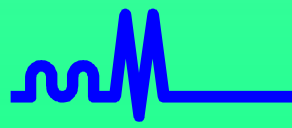
- Automated quantitative data mining
- Human assessment
  - National Pharmacovigiolance Centres
  - Review Panel
  - UMC staff

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 back-ground, using a Bayesian confidence propagation neural network (BCPNN)

Eur J Clin Pharmacol 1998;54:315-321



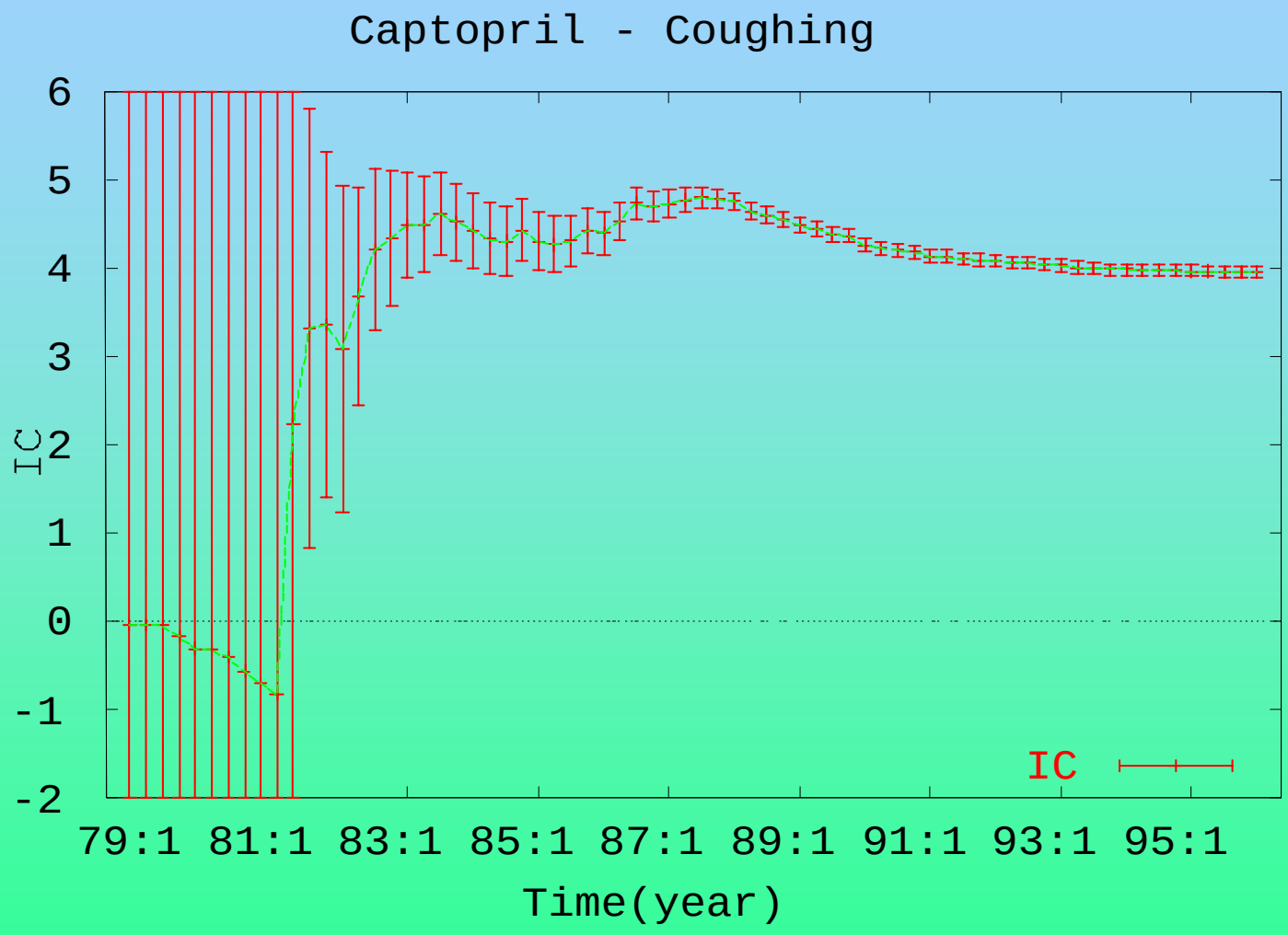
The BCPNN network is used to count:

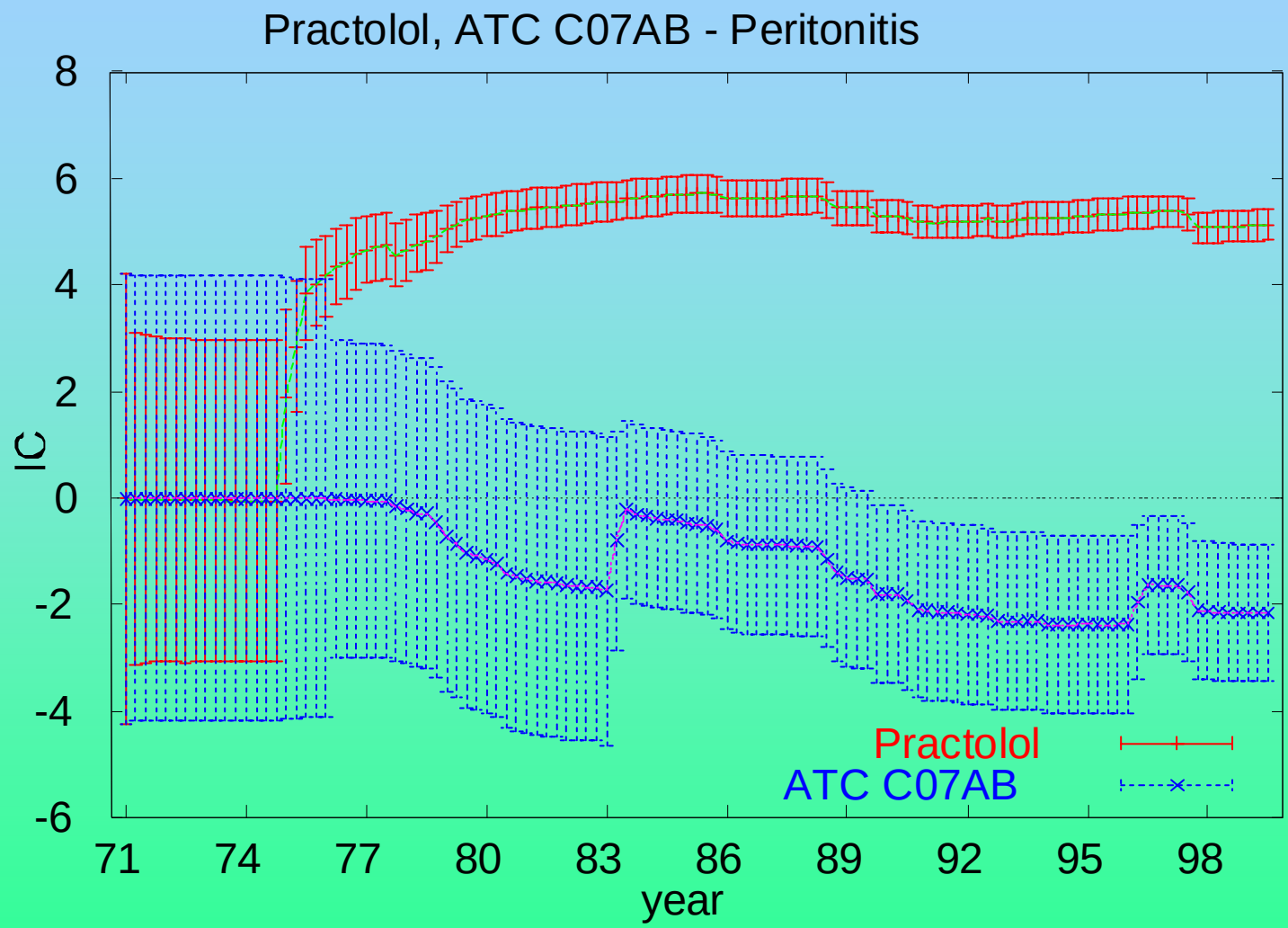
- All reports in the database
- All occurrences of variable x (e.g. ADR)
- All occurrences of variable y (e.g. drug)
- All occurrences of x and y together

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
6
5
4
3
2
1
0
-1
-2
IC
IC
79:1 81:1 83:1 85:1 87:1 89:1 91:1 93:1 95:1
Time(year)


Practolol, ATC C07AB - Peritonitis
IC
year
8
6
4
2
0
-2
-4
-6
71
74
77
80
83
86
89
92
95
98
Practolol
ATC C07AB

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?

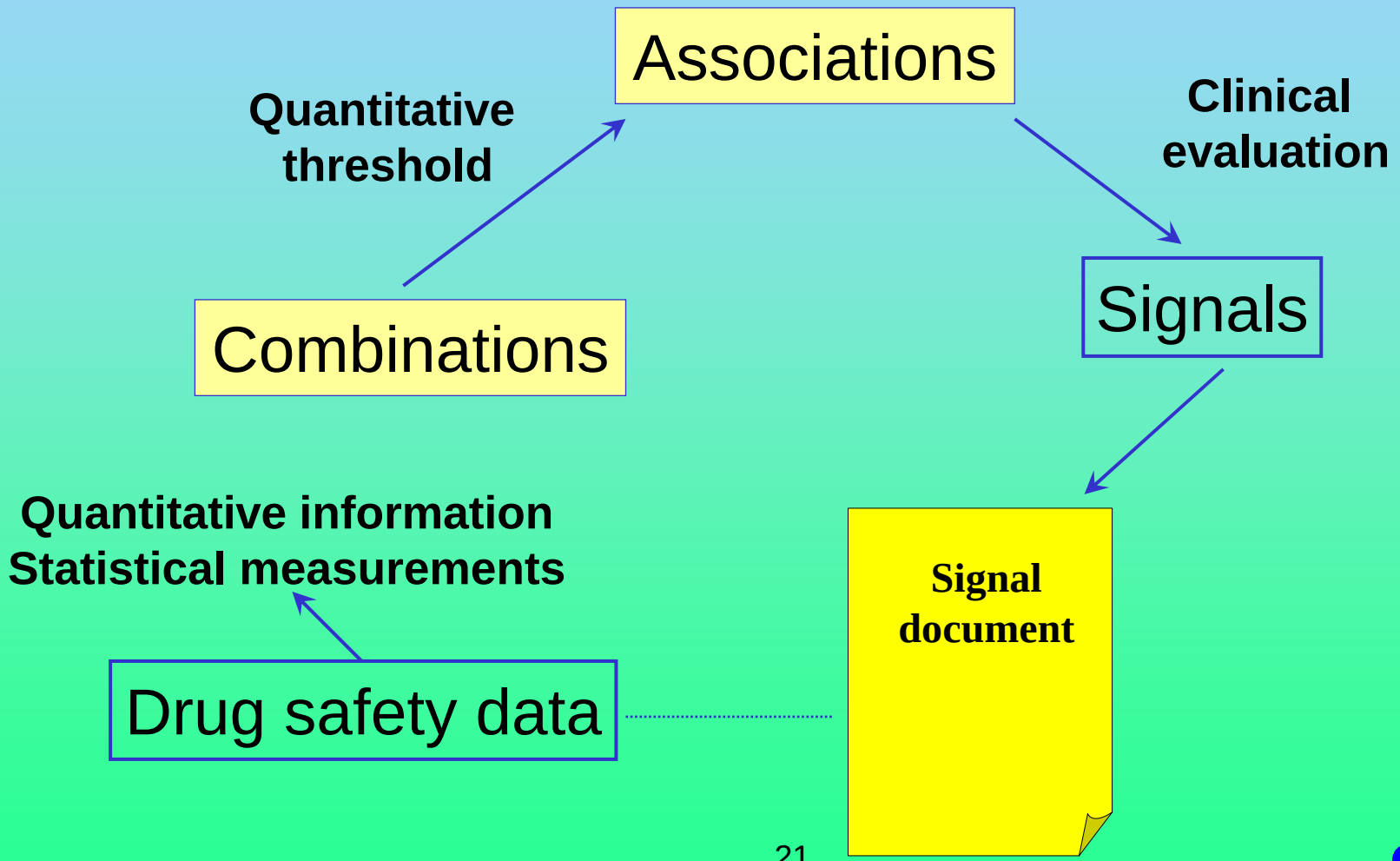
Associations Database

- 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?

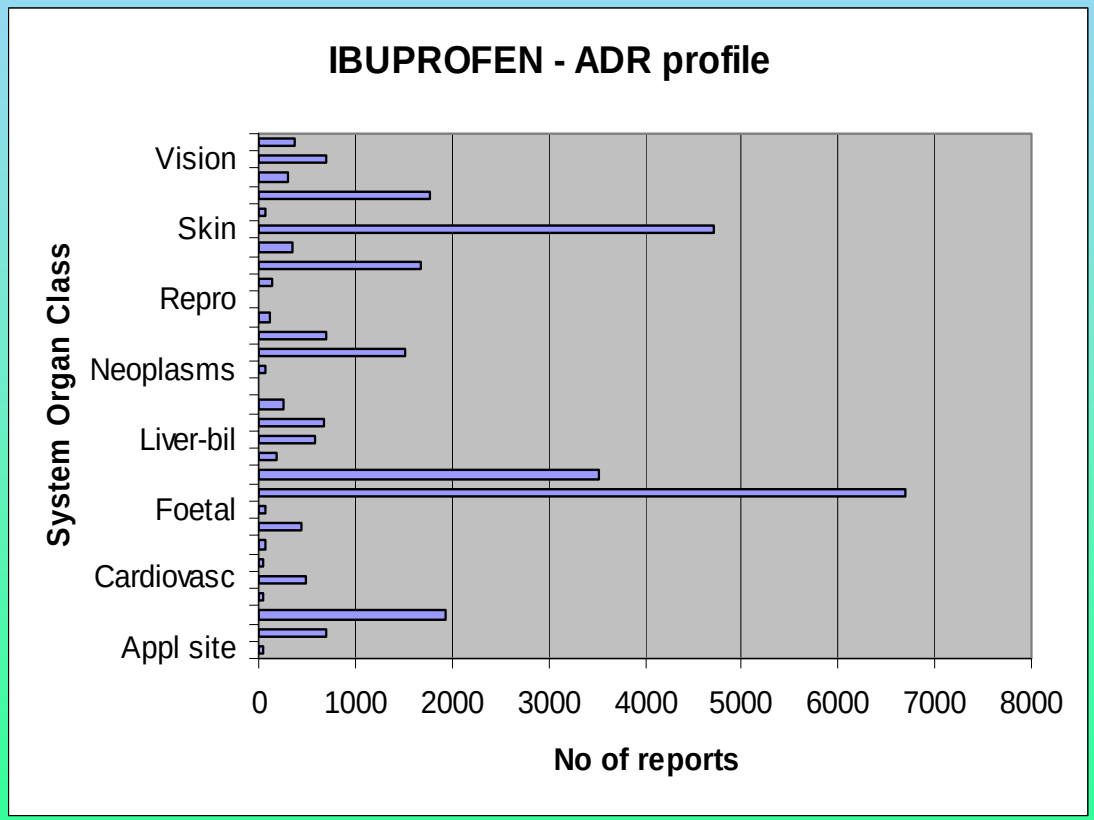
- Signals should not be missed
- Signals should be found early
- ‘False’ signals should be kept to a minimum

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, Uppsala, Sweden

No. 1, 2001

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). This text provides a summary of the WHO position on this vaccine. This is a significant departure from the well-defined role of WHO to facilitate the exchange of information. In the last editorial we said 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.

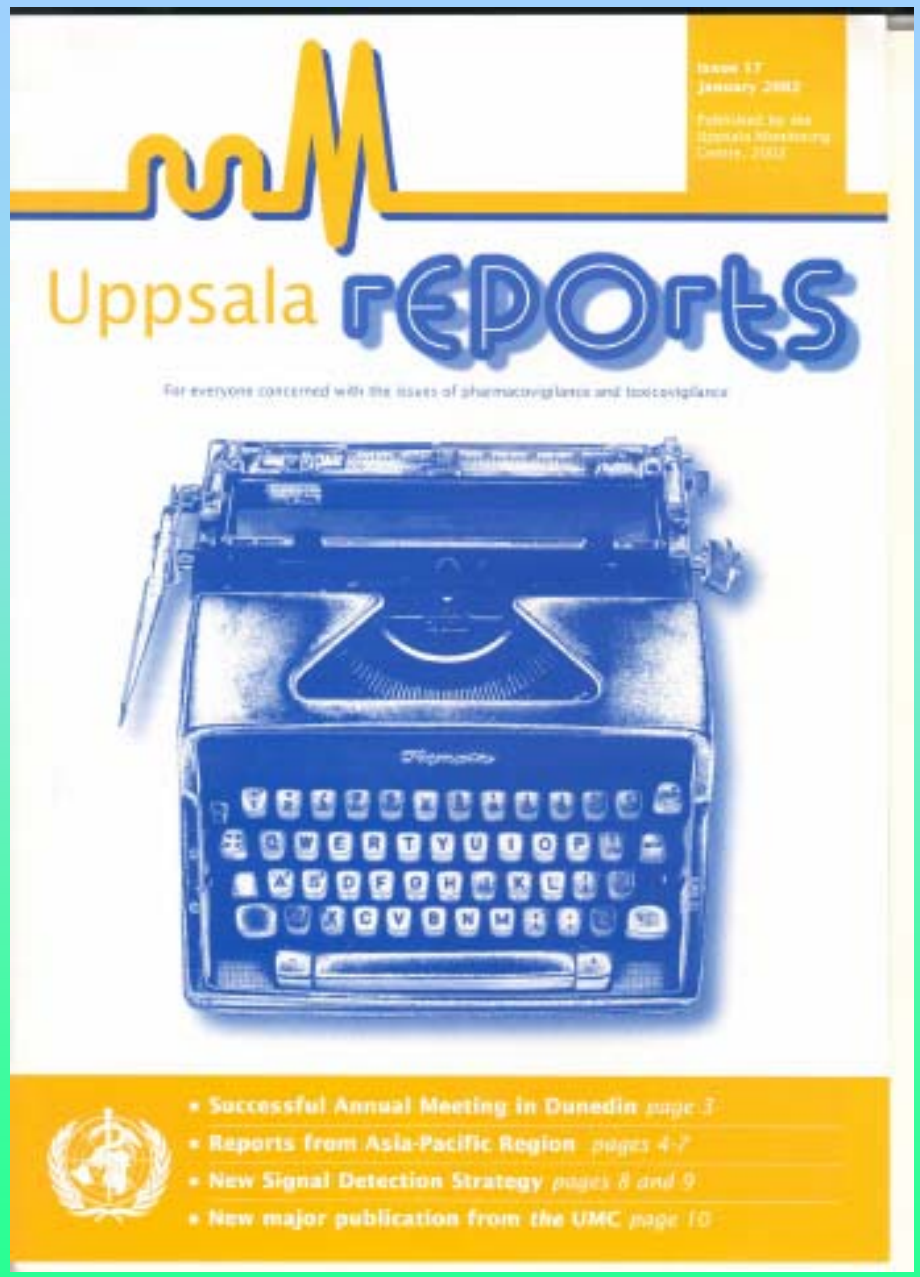
Contents ■
Regulatory matters ■
Safety of Medicines ■
Medication errors ■
Feature: MMR vaccine ■

Useful Internet addresses:

The Therapeutic Goods Administration in Australia has created a Webpage on Prescribing medicines in pregnancy:
http://www.health.gov.au:80/tga/docs/html/mipmedicine.htm

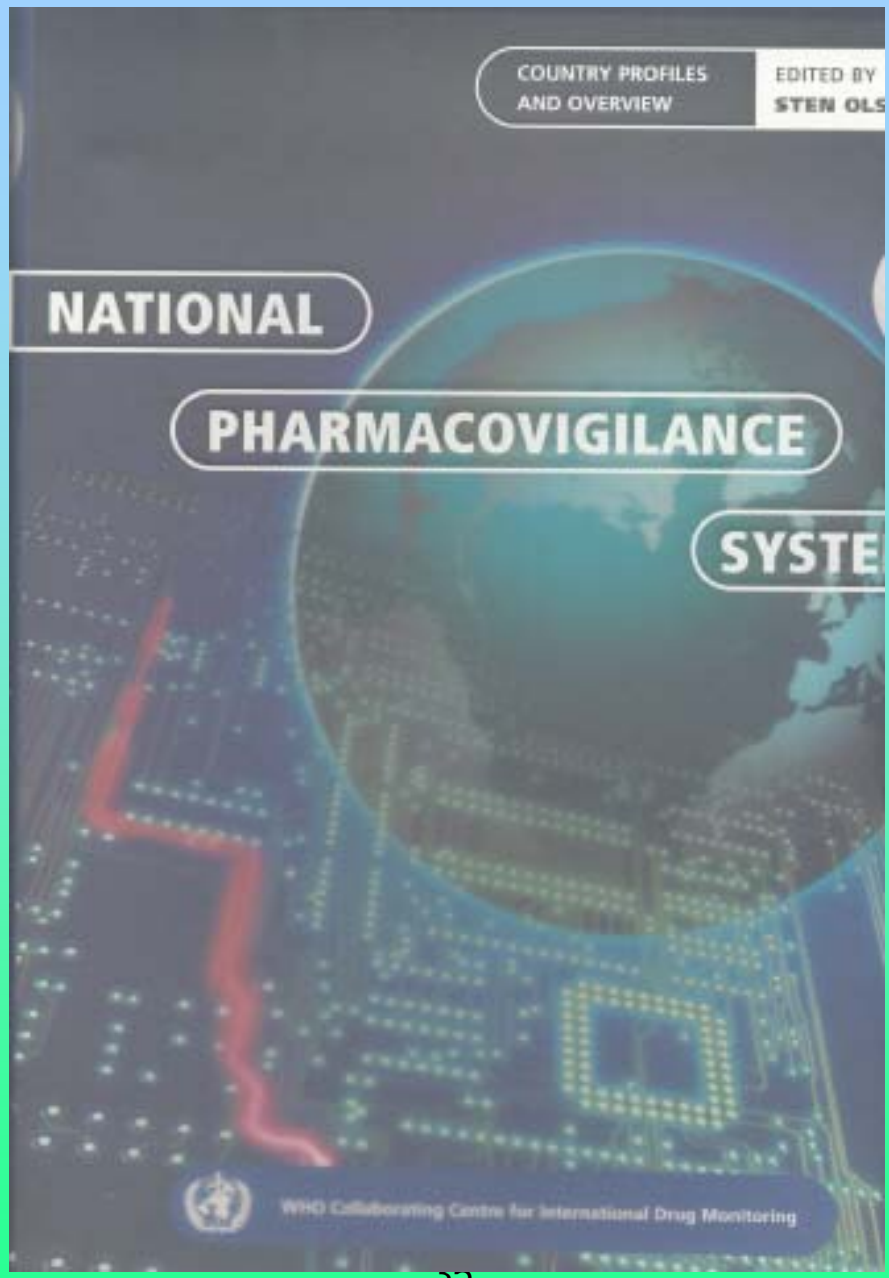
The US Pharmacopoeia webpage includes information and links on veterinary medicines as well as human medicines including medication errors (see p. 7):
http://www.usp.org/

12


Issue 17
January 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

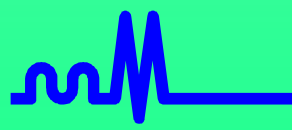
Training and technical support

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


COUNTRY PROFILES
AND OVERVIEW
EDITED BY
STEN OLS
NATIONAL
PHARMACOVIGILANCE
SYSTE
WHO Collaborating Centre for International Drug Monitoring

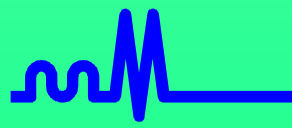
UMC involvement in local activities, 1998 - 2002

- 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



WORLD HEALTH ORGANIZATION

Drug Safety Pharmacovigilance

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 to15-20% 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

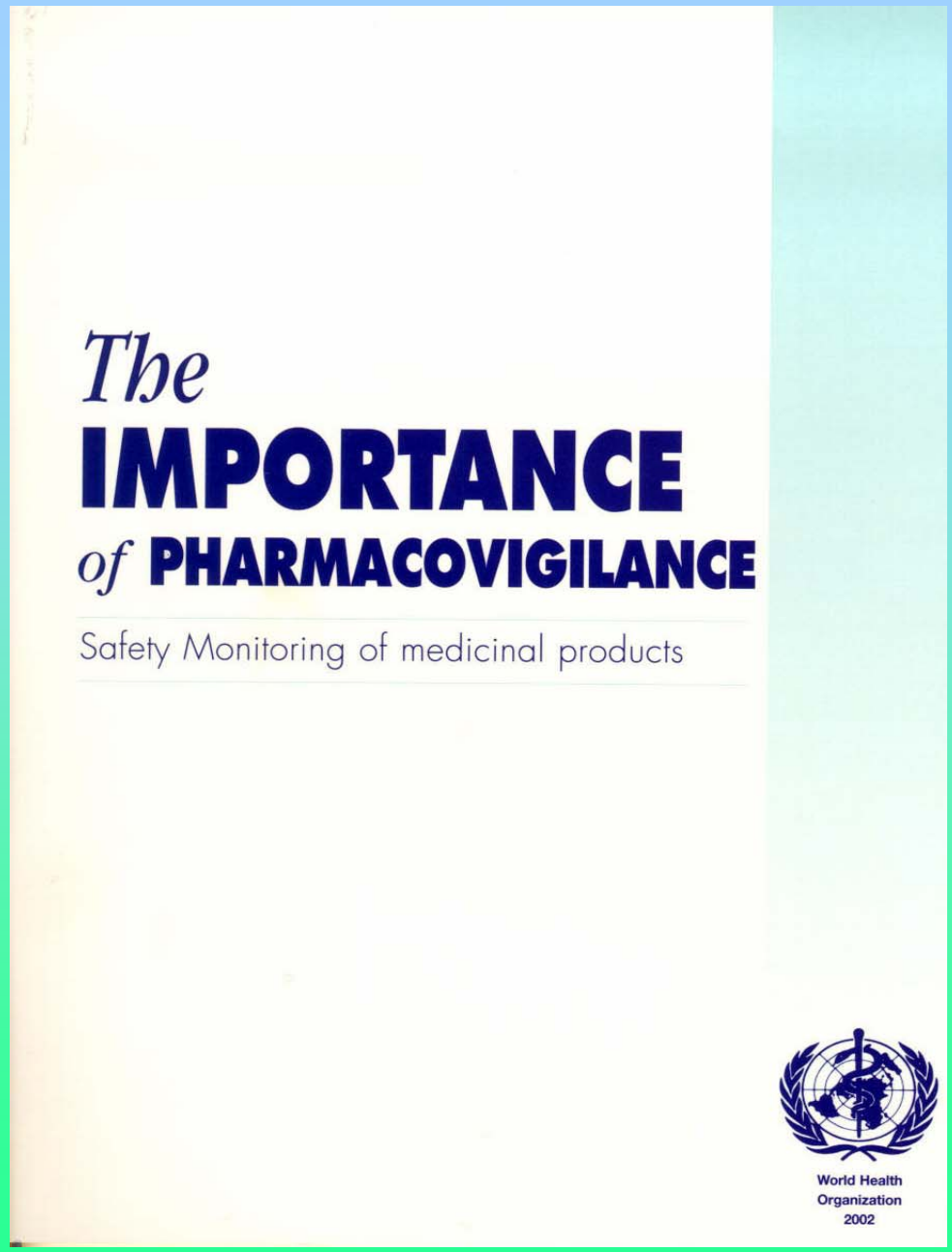
Pharmacovigilance service

- ❑ 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 pharmaco-therapy 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 UPPSALA MONITORING CENTRE


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: 0114-9916
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
adis
INTERNATIONAL
AUCKLAND • BUENOS AIRES • CHESTER • HONG KONG • MADRID
MILAN • OSAKA • PARIS • PHILADELPHIA • SÃO PAULO • SYDNEY

Reactions weekly

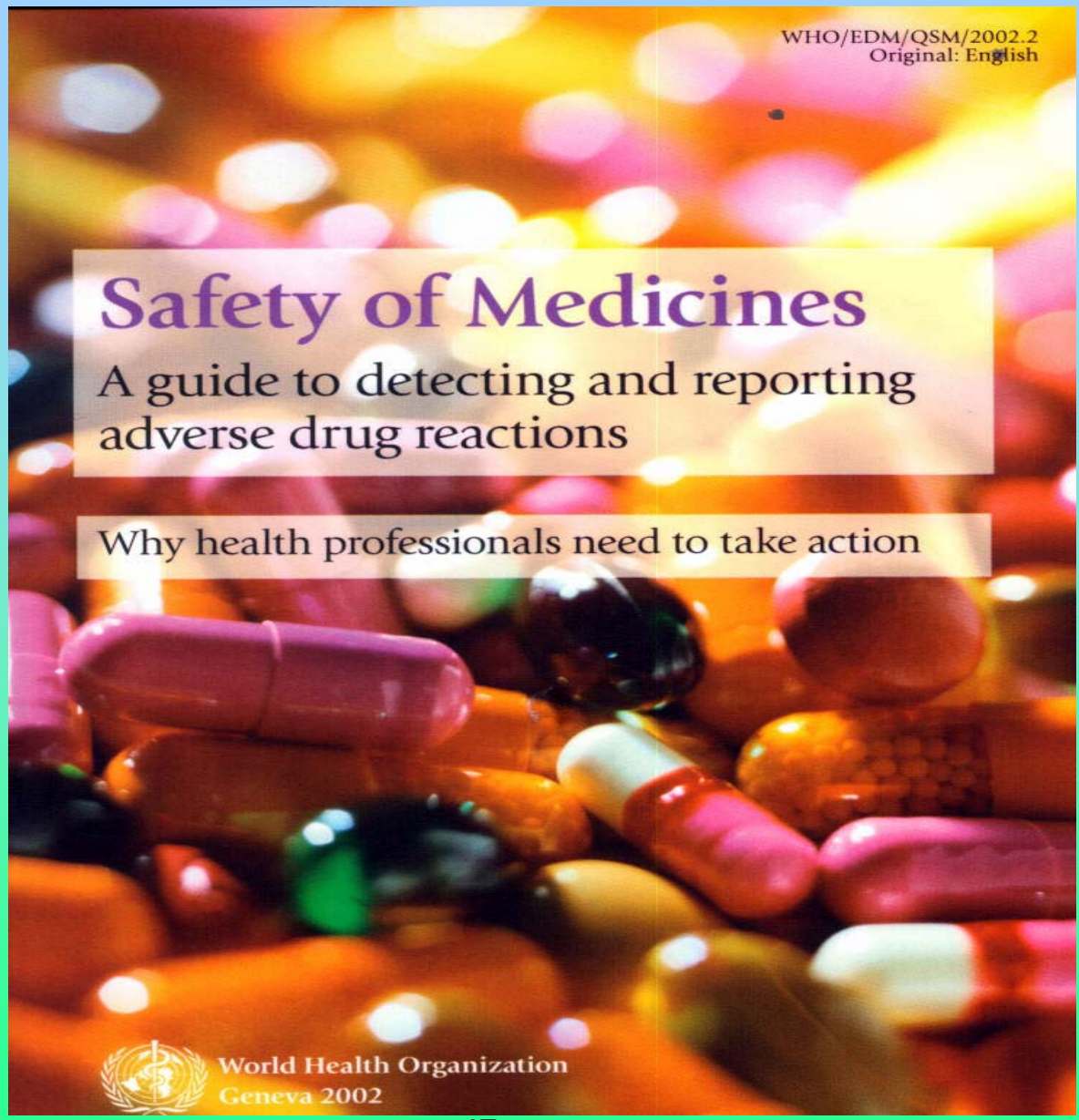
Including the Adverse Reactions Newsletter from the Uppsala Monitoring Centre

23 Feb 2002 No. 890

HIGHLIGHTS

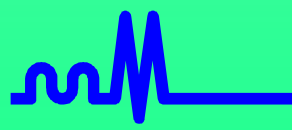
The UPPSALA MONITORING CENTRE

adis INTERNATIONAL


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

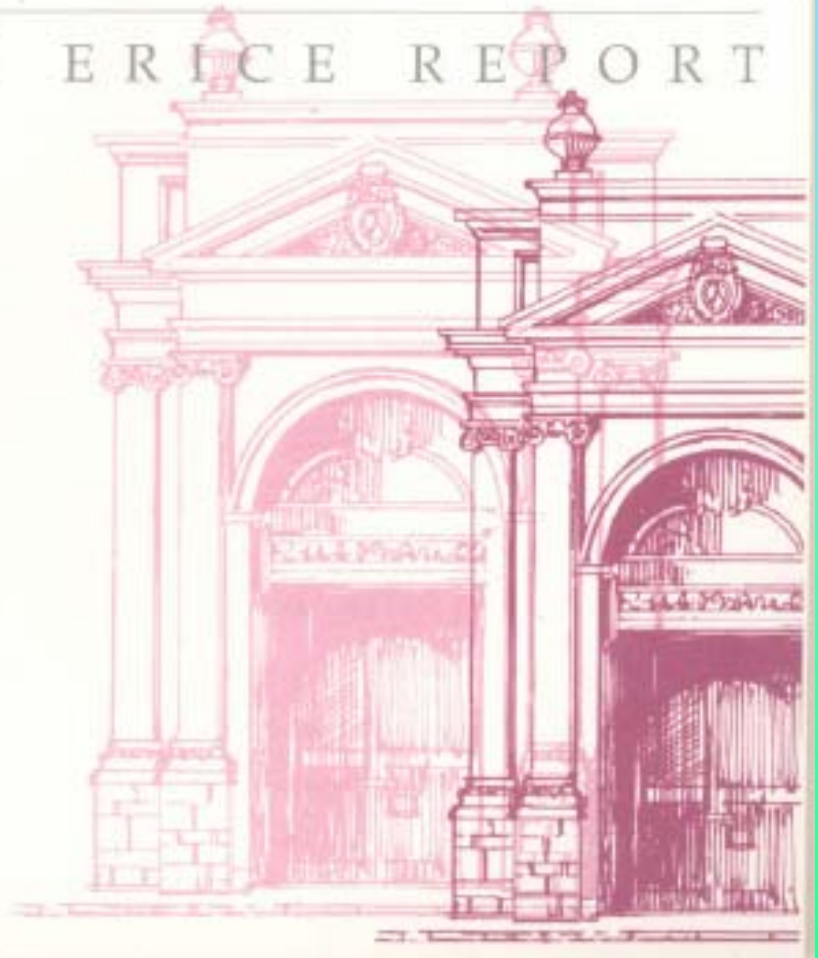
Research and development

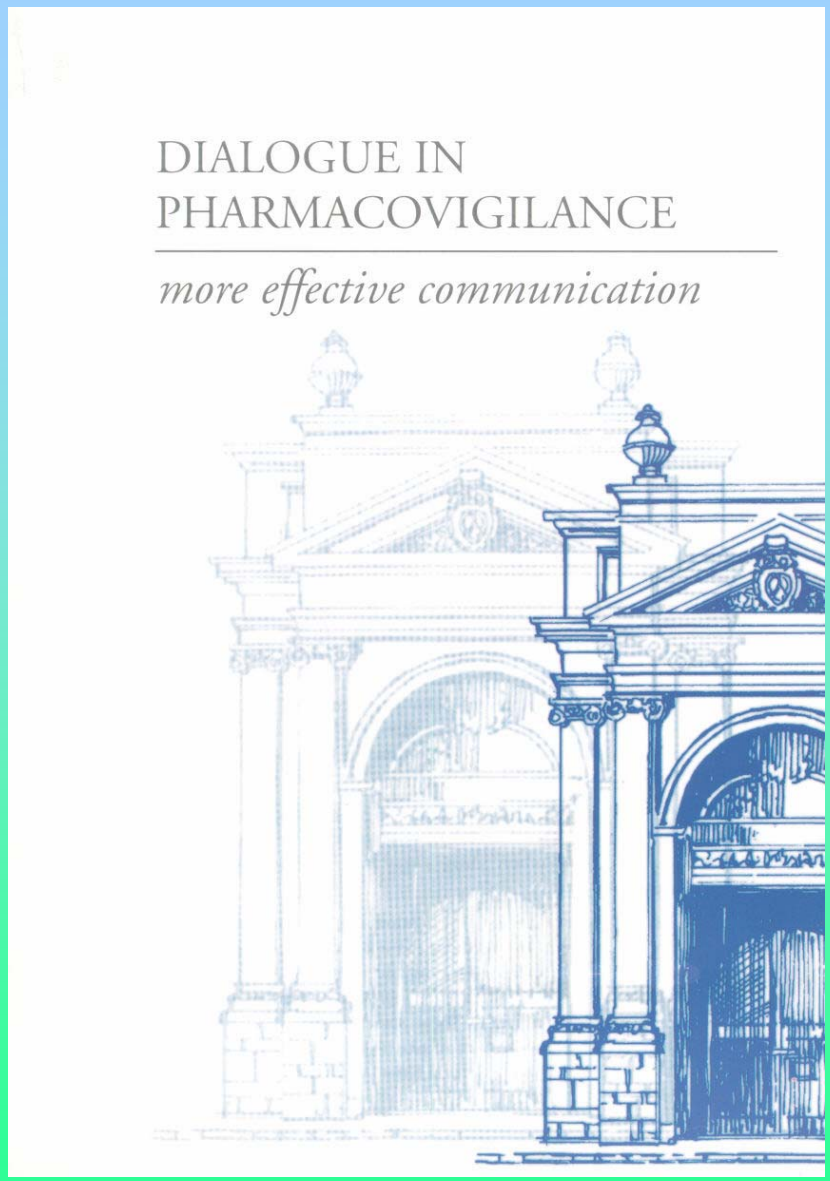
- Methods for signal identification and analysis; complex connections
- Improved monitoring of herbal or traditional medicines
  - collaboration with Royal Botanical Gardens, Kew, UK
- Good communications practice in pharmacovigilance; collaboration with:
  - University of Verona
  - CIOMS

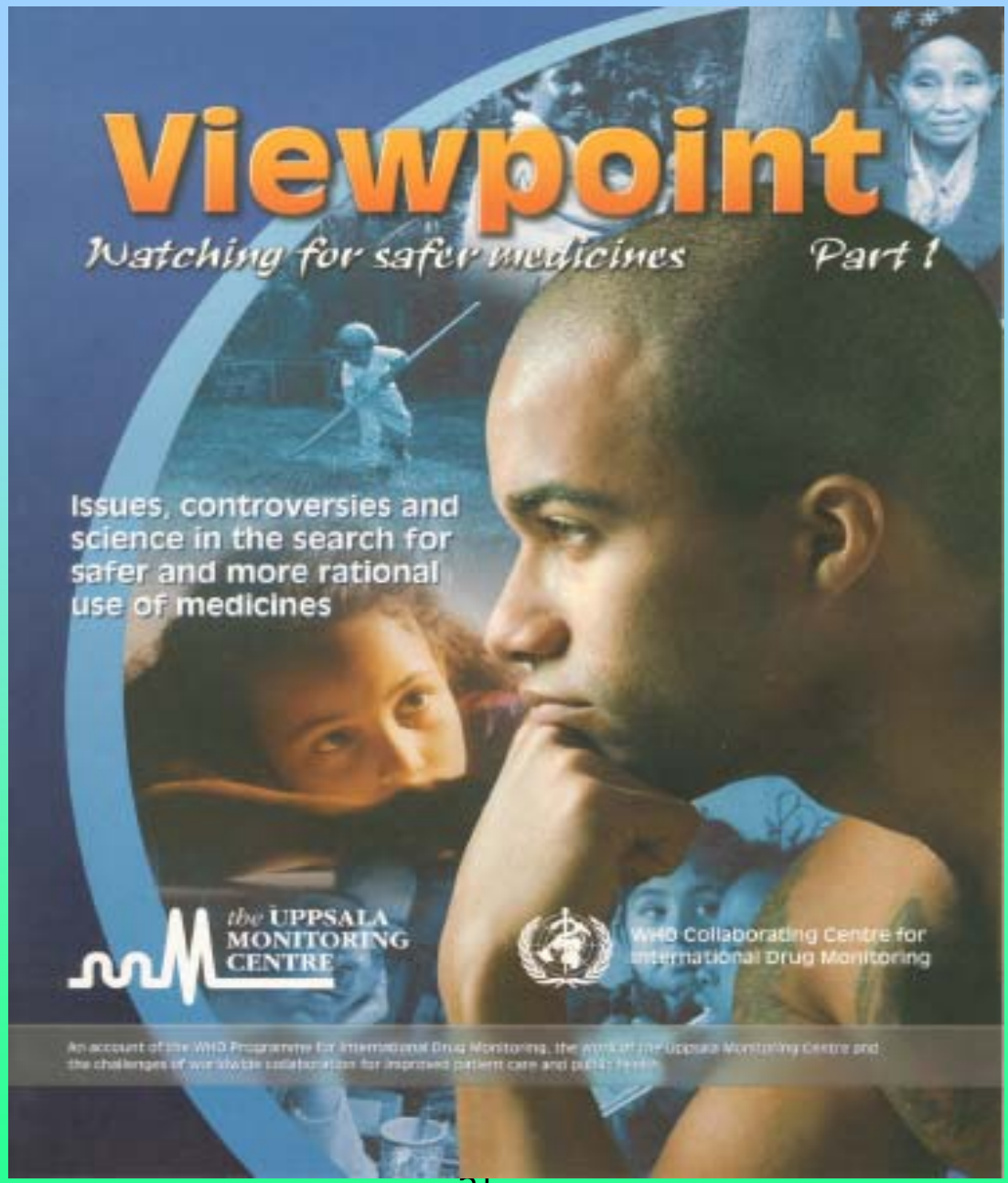


EFFECTIVE COMMUNICATIONS IN PHARMACOVIGILANCE

THE ERICE REPORT




DIALOGUE IN
PHARMACOVIGILANCE
more effective communication


Viewpoint
Watching for safer medicines
Part I
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

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

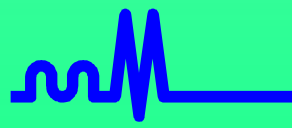
Eg. Herbal remedies for treatment of peptic ulcer A02W

A02WA (containing saponins)

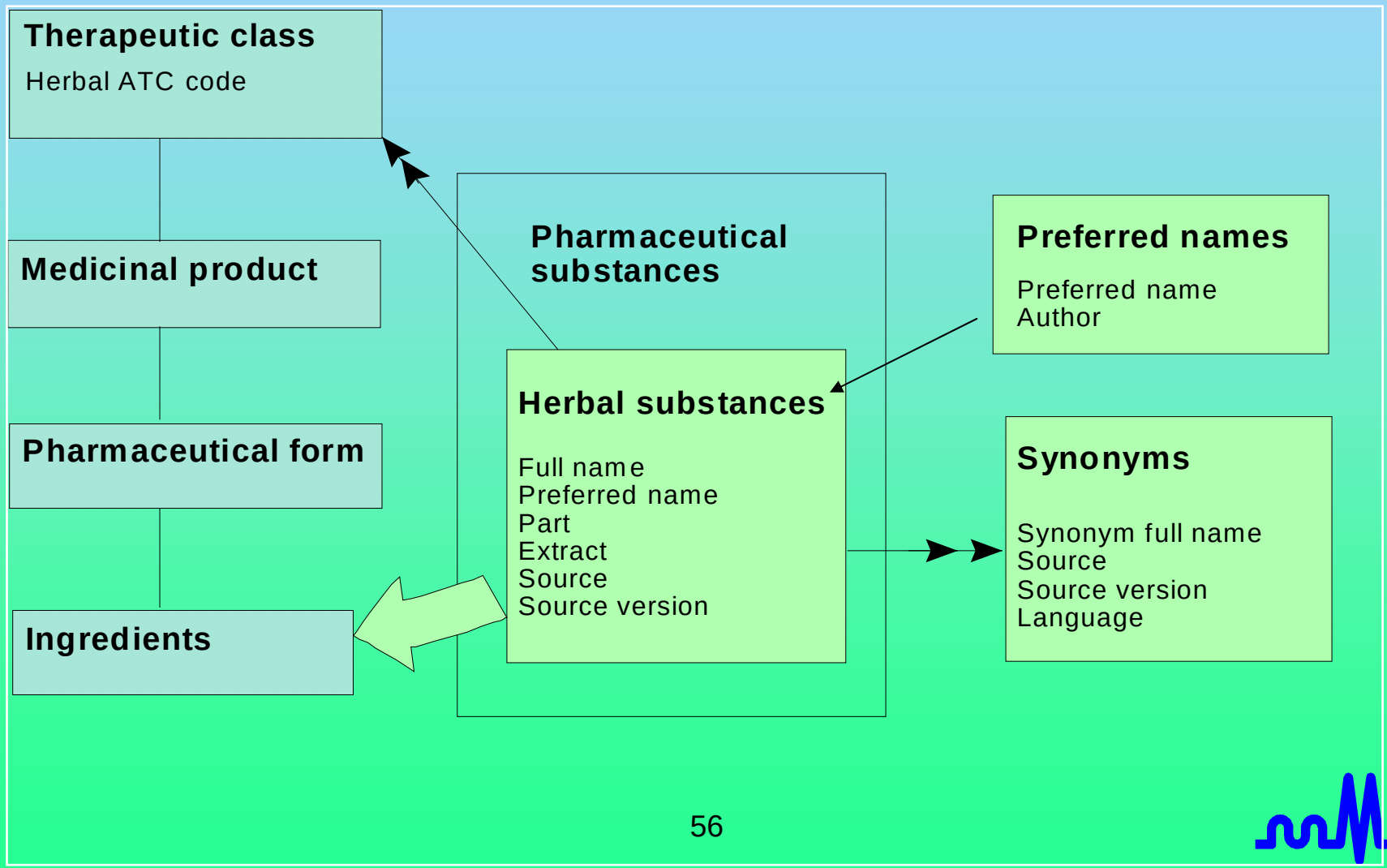
A02WB (containing mucilage)

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

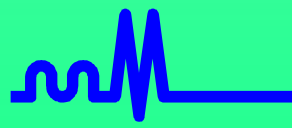
Data available to non-members

- 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 treament 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