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The Role of the WHO Programme on International Drug Monitoring in Coordinating Worldwide Drug Safety Efforts

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Abstract

The rationale for setting up the WHO International Programme for Adverse Reaction Monitoring, 30 years ago was to make it possible to identify rare adverse drug reactions (ADRs) that could not be found through clinical trial programmes. It became evident that maintaining an international database of ADR case reports and a network of institutions and scientists concerned with drug safety issues provides great additional gains when compared with operating in isolation. Thus, the scope of the WHO programme has expanded over time to accommodate the expansion of the field of drug safety monitoring, now often named pharmacovigilance. The international centre, the WHO Collaborating Centre for International Drug Monitoring in Uppsala [now known as the Uppsala Monitoring Centre (UMC)], maintains the international database and serves the national centres associated with the WHO programme; however, the role of the centre is expanding allowing it to play a leading role in global drug safety monitoring.

The national centres are appointed by the governments of each of the countries participating in the WHO programme. These centres are responsible for collecting spontaneous ADR reports originating from health professionals. 49 countries are currently contributing case information and are full members of the programme; an additional 11 countries have applied for membership but have still not submitted any reports. The annual influx of reports is currently fluctuating at around 150 000 reports.

In its development, the data collected by the WHO programme was guarded by strong rules of confidentiality. In some member countries, however, case data, with the important exception of reporter and patient identities, has always been public information. The UMC has made it a priority to try to create an atmosphere of openness and trust between all parties involved in drug safety assessment, which will eventually enable general sharing of available data and an extended analysis and use of the data collected. The WHO network represents the wealth of competence and experience that is at the disposal of countries wishing to join the international pharmacovigilance community.

Table I. Countries collaborating in the WHO International Programme for Adverse Reaction Monitoring, as of April 1998

Country	Year of entry
Member countries	
Argentina	1994
Australia	1968
Austria	1991
Belgium	1977
Bulgaria	1975
Canada	1968
Chile	1996
China	1997
Costa Rica	1991
Croatia	1992
Cuba	1994
Czech Republic	1992
Denmark	1968
Finland	1974
France	1986
Germany	1968
Greece	1990
Hungary	1990
Iceland	1990
India	1998
Indonesia	1975
Ireland	1968
Israel	1973
Italy	1975
Japan	1972
Korea	1992
Malaysia	1990
Morocco	1992
The Netherlands	1968
New Zealand	1968
Norway	1971
Oman	1995
Philippines	1995
Poland	1972
Portugal	1993
Romania	1976
Russia	1997
Singapore	1993
Slovak Republic	1993
South Africa	1992
Spain	1984
Sweden	1968
Switzerland	1991
Tanzania	1993
Thailand	1984
Tunisia	1993
Turkey	1987
United Kingdom	1968

The rationale for setting up the WHO International Programme for Adverse Reaction Monitoring 30 years ago was to make it possible to identify rare adverse drug reactions (ADRs) that could not be found through clinical trial programmes. Collecting ADR case reports from as many drug exposures as possible into a single database will, at least theoretically, provide optimal conditions for finding new adverse reaction signals at the earliest possible time.

It soon became evident that maintaining an international database of adverse reaction case reports and a network of institutions and scientists concerned with drug safety issues provides great additional gains when compared with operating in isolation. The scope of the WHO programme has consequently expanded over time to accommodate the expansion of the field of drug safety monitoring, now often named pharmacovigilance.

The international centre created under the auspices of the WHO was originally set up to maintain the international database and to serve the national centres associated with the WHO programme. Over time, pharmacovigilance has become the concern of many parties in society and merely responding to the information needs of national pharmacovigilance centres is no longer sufficient if the WHO centre is to play a leading role in global drug safety monitoring currently and in the future. This paper is intended to provide a personal view on what the role of the WHO drug monitoring programme is today and how it is likely to develop in the immediate future.

1. Programme Setup and Mission

WHO headquarters in Geneva is responsible for the WHO drug monitoring programme. Operational aspects are managed by a Swedish foundation named the WHO Collaborating Centre for International Drug Monitoring in Uppsala (now known as the Uppsala Monitoring Centre, UMC) according to an agreement signed between WHO and Sweden in 1978. The only regular budget contribution to the Centre is provided by the Swedish government.

Table II. Countries that have applied for membership of the WHO International Programme for Adverse Reaction Monitoring, as of April 1998

Armenia
Cyprus
Egypt
Estonia
Iran
Macedonia
Pakistan
Sri Lanka
Vietnam
Yugoslavia
Zimbabwe

In each country participating in the WHO programme there is a national centre, appointed by the government, responsible for collecting spontaneously reported suspicions of ADRs, originating from health professionals. National centres transform their case reports into a specific WHO format and submit them to the UMC on a regular basis. 49 countries are currently contributing case information and are therefore considered full members of the programme (table I). An additional 11 countries have applied for membership but have still not submitted any reports (table II). At the UMC, reports are checked for technical accuracy and are then entered into the WHO database. Every week new reports are added to the database and, as of January 1998, the database consisted of 1.8 million cases. The annual influx of reports is currently fluctuating at around 150 000 reports.

The mission of the UMC is to promote rational drug therapy by:

- collecting and analysing information about drug safety at the international level
- collecting, classifying and disseminating information about national activities concerning drug safety
- developing professional and scientific expertise to improve the analysis of international questions concerning drug safety
- developing methods for use in work within drug safety and neighbouring fields
- supporting the development of standards for the assessment of risk and beneficial use of drug therapy
- contributing to the improvement of communication and education for relevant interest groups concerning risks and advantages with drug treatment
- contributing, on request, to the development of methods for international application within fields closely linked to drug safety.

In practical terms the mission of the UMC translates into activities in the following specific areas:

- collection of ADR reports on a worldwide scale and maintenance and use of the international database
- dissemination of information
- education and advice
- research and development
- international harmonisation.

2. Routine Use of the WHO Database

2.1 Signal Identification and Review

The UMC has developed a set of computer programmes by which the incoming information from participating centres is screened every 3 months. Various kinds of listings are produced as a result of this screening and these listings are distributed to national centres for review. The UMC has also set up an international panel of approximately 30 expert consultants who are assisting the centre in identifying new and clinically important adverse reaction signals within their specific area of expertise. Each consultant receives a subset of suspected drug reactions that are identified by the computer system as being new or potentially serious. The consultant selects and looks deeper into the potential drug problems that he/she judges as being of greatest clinical relevance and writes short statements based on the available information. These statements are distributed regularly to national centres as a document called 'Signal' to be evaluated and acted upon according to the discretion of

each centre. A recent survey demonstrated that these signals are actively used and appreciated by national centres.[1]

When considered warranted, signals identified are written up and submitted to medical journals for publication.[2-15] Published signals are based on information originating from several different countries, which testifies to the validity of the approach of collecting case information from many countries into 1 single database.

The present system of signal identification and review is by no means perfect, as indicated by the recently revealed association between heart valve disorders and administration of fenfluramine/dexfenfluramine and phentermine which was first reported to the WHO from Belgium in 1989 to 1996, but which was only identified as a signal in the US in mid-1997.[16]

Examples of problem areas are as follows:

- *Delay in reporting.* Although the WHO database is updated weekly there is a considerable variation in the frequency of submitting reports from national centres, ranging from every 2 weeks to once per year.
- *Incompleteness of the database.* A variable degree of underreporting is an inherent problem in spontaneous adverse reaction monitoring. An additional complication is that the WHO database does not properly reflect drug problems experienced in countries without any or with only poorly operating adverse reaction reporting systems. Some countries have taken deliberate decisions not to submit certain types of reports e.g. those obtained from industry, relating to herbal remedies or considered to be doubtful in terms of causality.
- *The vast number of potential signals.* Because the WHO Programme is focussed on being as sensitive as possible in the production of new signals, the international database produces in the order of 10 000 potential signals per annum as listed in the 'New to the System' output document. Many of these associations are random observations that are regarded as background 'noise'. The challenge is to select the important few out of a continuous flow of insignificant drug reaction associations reported.[17]
- *Often case details supporting the drug-reaction association are scarce which makes causality assessment difficult.* The UMC has created a system by which all reports in the database are classified according to the amount of information provided. The 4 grade scale allows assessors to concentrate on associations supported by a reasonable amount of data.
- *Limited resources for medical assessment of potential signals.* Drug safety officers operating from national centres put priority to safety issues being discussed in the national forum. They are very rarely concerned with a proactive analysis of international data, although such a shift in focus could lead to earlier problem identification and prevention of drug safety problems. The consultants presently commissioned by the UMC to undertake signal review are volunteers, doing their task on extra time, without pay.

National pharmacovigilance centres in major countries with a reasonably good reporting rate are in a more favourable position than the WHO programme to identify new adverse reactions occurring with a fairly high frequency, since they receive the reports first and are closer to the reporter and the patient. The role of the international system is to concentrate on the rare (below 1/1000) but clinically significant reactions where pooling of international data is most likely to increase the chance of detection.

In the early phases of the WHO drug monitoring programme attempts were made to create computer programmes that would produce more or less automatic signals of new and unexpected reactions through statistical processing of the database.[18] However, the results in terms of production of information on new, clinically relevant adverse effects were rather disappointing. Today we have reason again to be optimistic about the statistical approach since new methodology and more powerful computers have become available. This methodology, when further developed, will be a tool by which the complex pattern of factors influencing

the risk for an individual patient to acquire a certain type of adverse reaction when exposed to a certain drug, may be explored.

Another important new approach in signal analysis is the combination of ADR reporting rates with information on drug utilisation and demographic data on an international level. This is made possible through a collaboration between the UMC and the commercial company Intercontinental Medical Statistics (IMS) the only source available for drug utilisation statistics comparable between countries. The method allows for a rapid crude assessment of incidence rates of reported associations.[15,19-22]

2.2 Using the WHO Database as a Reference Source

National centres, pharmaceutical companies and other interested parties are given access to the unique collection of adverse reaction reports that the WHO database represents. It can be used in a variety of situations, for example:

- to provide support or doubt on a suspected drug/reaction association reported in a single case (signal strengthening)
- to display the adverse reaction profile of a drug or a class of drugs either as represented in the whole database or divided by country. Country differences in reporting are easily examined
- to follow the continuous flow of adverse reaction data, e.g. to be presented in a Periodic Safety Update Report as recommended by Council for International Organisations of Medical Sciences (CIOMS) II and the International Conference on Harmonisation (ICH) working party E2C
- to collect a cohort of patients experiencing the same type of drug reaction in search for common factors that might give a clue to the underlying mechanism.

The UMC offers retrievals in the WHO database either as a consultancy or as an on-line service. National centres have unrestricted access to all information in the database. Other interested parties can, however, only have access to individual case reports from the approximately 30 countries that today have consented to the release of such data to any inquirer.

3. Dissemination of Information

In addition to providing national centres with feed-back regarding case reports that have been submitted to the WHO database, the UMC tries to keep track of all kinds of information from around the world regarding drug safety and to disseminate the collected information to its various clients. The main channels presently used by the UMC for dissemination of information are:

- *The Adverse Reaction Newsletter*. This is issued 4 times a year, containing short reviews of drug problems raised in national ADR bulletins, regulatory actions based on safety concerns, communications on studies being undertaken or papers published by national centres. The newsletter is distributed to national centres and a limited number of other parties nominated by national centres.
- *Uppsala Reports.* This is issued 3 to 4 times a year to all clients and customers of UMC services. This newsletter contains information related to developments within the WHO programme and pharmacovigilance in general that is not related to specific drug problems.
- *The UMC Internet home page.* This can be found at http://www.who.pharmasoft.se and presents the centre, its mission, its products and services and upcoming events. Also *Uppsala Reports* and a special version of the *Adverse Reactions Newsletter* are available through the home page. Since the use of Internet in general is expanding rapidly in all quarters around the world, development of services for provision over Internet will be a major expansion area for the WHO programme in the years to come.
- *An e-mail discussion group called 'vigimed'.* Membership in this discussion group is restricted to persons connected to national centres. Vigimed allows immediate distribution of messages between centres that have access to e-mail, contributing to rapid exchange of infor-

mation between drug regulators around the world in drug safety matters.

Resources at the UMC do not allow the provision of full coverage of the world literature relevant to drug safety matters. There are other excellent sources available for this kind of information, e.g. *Reactions Weekly.*

In the early development phase of the WHO drug monitoring programme, collected data was guarded with strong rules of confidentiality, motivated by the fear of misinterpretation of unproven drug/reaction associations. In some member countries, however, case data, with the important exception of reporter and patient identities, has always been public information protected by 'freedom of information' legislation. Only slowly and gradually has the WHO programme been able to get away from a situation of complete confidentiality of collected data towards others than participating national centres. Some countries still prefer not to allow release of their ADR case reports to others than national centres. The UMC has made it a priority to try to create an atmosphere of openness and trust between all parties involved in drug safety assessment, which will eventually enable general sharing of available data, and an extended analysis and use of the data collected.[23-24]

4. Education and Advice

The UMC has developed a training course in adverse reactions and adverse reaction monitoring aimed at providing new staff at national centres and health professionals in the process of starting such centres with basic training in pharmacovigilance. This 2-week course was carried out annually in Uppsala for 4 years, 1993 to 1996, but is now being turned into a bi-annual event. Regional courses in various parts of the world are now interspersed with the Uppsala courses. Course programmes and faculties for the regional courses are developed as a joint effort by the UMC, WHO Geneva and the local organiser. In a separate effort, work has started, together with Department of Pharmacology, Therapeutics and Toxicology, University of Wales, Cardiff, in developing a material for distance training in pharmacovigilance, with the aim of connecting it to an academic setting. An academic connection is also provided by the new WHO Reference Centre for Pharmacovigilance Information and Training at Department of Pharmacology of the University of Verona, Italy, which will assist the UMC in development of education and information activities.

On request, UMC staff members visit countries to investigate the conditions for setting up an adverse reaction monitoring programme and to provide a plan of action for its implementation. Guidelines for setting up and running a national pharmacovigilance centre have been developed through a combined effort of WHO headquarters and the UMC. The UMC has also collected information on the operating procedures of national programmes, compiled country profiles and an international overview, issued in the publication *National Pharmacovigilance Systems.*[25] The second revised edition is published in 1998 and regular updates will be provided.

Promotional and educational material used in support of national adverse reaction monitoring programmes are being collected and compiled by the UMC. The material is presented to national centres as a source of inspiration and ideas for further improvement of national campaigns to intensify the reporting of adverse drug reactions. Further efforts will be made in developing general promotional aids to encourage adverse reaction reporting, aids that can be adapted to the local situation in each country.

The WHO has an important role to play in providing motivation, inspiration and technical competence to member countries who do not yet have a structure for systematic collection of information regarding drug safety. The WHO network represents a wealth of competence and experience that is at the disposal of countries wishing to join the international pharmacovigilance community. It is important to understand that drug safety problems frequently differ between countries, leading to a need for each country to monitor its own situation. It is not advisable for any country to rely solely on

data made available from different setups, or on decisions made in other countries. On the other hand, no country can safely rely only on information from its domestic information base.[26]

Activities in this field during the 1990s have been rather successful as judged by the number of countries joining the WHO programme. Through the recent connection of China, India and Russia to the programme the potential input to the system and the outreach of information from the system has expanded enormously.

5. Research and Development

Guiding principles in choosing direction for research and development have been to extend and refine the use of the WHO database and to develop tools and systems which can enhance the efficiency of operations of national centres and other parties involved in the analysis of drug safety data. The strategy has been to develop alliances with centres of excellence in each specific area. Main areas of research and development at present are as follows:

- *Bayesian neural networks for identification and analysis of adverse reaction signals.* This is a joint project with the Royal Institute of Technology in Stockholm which has produced some promising results.[27] Basically the method provides a quantitative measure of the strength of association of a drug/reaction combination in the database. Combinations occurring more frequently than expected as compared with the generality of the database are highlighted. The method requires access to considerable computing power, but makes full use of the huge WHO database in that the overall reporting rates create the baseline for what is expected. The confidence limits for 'expectedness' can be chosen at will to set the sensitivity of the methodology. The method has been put in routine use at UMC but the field is open for further research and development.
- *Classification and improved monitoring of herbal preparations.* Nomenclature for herbal products is very confused and claimed indications for their use are often culture dependant. These factors have made classification and sorting of adverse reaction reports involving herbal remedies difficult, resulting in less than optimal signalling. A collaboration with the Royal Botanical Gardens, Kew and the University of Exeter, UK, have started with the aim of defining a nomenclature for medicinal plants and to work out a classification system compatible with the Anatomical Therapeutic Chemical classification system, endorsed by WHO for chemical drugs. In this area, the assignment of consultants from various parts of the world, representing different healing cultures, is of particular importance.
- *Development of an adverse reaction database according to the requirements of CIOMS 1A and the ICH E2B working parties.* This development is carried out in collaboration with the software company PharmaSoft in Uppsala and aims at allowing much more information on the individual case to be stored in the WHO database. Facilities for retrieval and presentation of data will be made more flexible than in the old database. Basic functions, including acceptance of reports in the E2B format, will be operational during 1998. A part of the project is to offer high-technology software for ADR report management at a low cost to small and newly established drug monitoring centres. The first offer for such a standardised management system was launched in December 1997.
- *Creation of links between terminologies for coding of adverse reactions.* Use of the WHO Adverse Reaction Terminology (WHOART) is mandatory when submitting case data to the WHO Programme. Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART) is another similar terminology previously used by the US Food and Drug Administration and many pharmaceutical companies. The Medical Dictionary for Regulatory Activities (MedDRA) terminology has recently occurred as a result of work in the ICH working party M1. The International Classification of Diseases

(ICD-10) is a dictionary frequently used in pharmacoepidemiological research. In continuation of the work previously performed in establishing links between WHOART and COSTART, the UMC is now embarking on a project to secure compatibility between WHOART and MedDRA and ICD-10. The aim is obviously to facilitate linkage of various drug safety databases and to enable transfer of information between them without major distortion.

- *Communications in pharmacovigilance.* In spite of major advances made in pharmacovigilance and pharmacoepidemiology in recent years, drug safety information provided to healthcare providers and patients is still largely unaffected by the progress made.[17] By calling together representatives of all major groups involved in the provision of drug safety information, the UMC and its partners is trying to identify practical steps that may be taken to improve communication in pharmacovigilance. A series of meetings have been held and research projects initiated with the aim of contributing to an atmosphere of openness and trust (see section 4). The so called Erice declaration on communicating drug safety information sets out the basis for further development in this area.[28,29] The declaration was drawn up at the International Conference on Developing Effective Communications in Pharmacovigilance which was held in Erice, Sicily, in September 1997. Participants from 30 countries agreed upon the following.
- Drug safety information must serve the health of the public. Such information should be ethically and effectively communicated in terms of both content and method. Facts, hypotheses and conclusions should be distinguished, uncertainty acknowledged, and information provided in ways that meet both general and individual needs.
- Education in the appropriate use of drugs, including interpretation of safety information, is essential for the public at large, as well as for patients and heath-care providers. Such education requires special commitment and resources. Drug information directed to the public in whatever form should be balanced with respect to risks and benefits.
- All the evidence needed to assess and understand risks and benefits must be openly available. Constraints on communication parties, which hinder their ability to meet this goal, must be recognised and overcome.
- Every country needs a system with independent expertise to ensure that safety information on all available drugs is adequately collected, impartially evaluated, and made accessible to all. Adequate nonpartisan financing must be available to support the system. Exchange of data and evaluations among countries must be encouraged and supported.
- A strong basis for drug safety monitoring has been laid over a long period, although sometimes in response to disasters. Innovation in this field now needs to ensure that emergent problems are promptly recognised and efficiently dealt with, and that information and solutions are effectively communicated.

6. Harmonisation

The WHO Programme contributes to development of common standards and methodologies in the area of drug safety monitoring chiefly by:

- developing definitions of words commonly used in pharmacovigilance[30]
- organising annual meetings of representatives of national centres in collaboration with WHO headquarters, Geneva
- maintaining tools commonly used in drug safety activities e.g. WHOART and the WHO Drug Dictionary (these tools are widely distributed to groups in the pharmaceutical industry and in academia who are concerned with recording of drug safety information)
- closely collaborating with other organisations involved in pharmacovigilance e.g. the International Society of Pharmacoepidemiology (ISPE), the European Society for Pharmacovigilance (ESOP), the Drug Information Asso-

ciation (DIA), CIOMS, and actively taking part in conferences organised by these parties.

7. Conclusion: Challenges Ahead

A number of recent political, administrative and scientific advancements have put the WHO Drug Monitoring Programme in a good position to maintain and extend its present role in pharmacovigilance. If the positive trend can be maintained, the UMC intends to focus its efforts on the following issues.

- *Improve reporting to the international centre.* The legal systems created in many countries lately have forced drug manufacturers to spend great resources distributing ADR cases submitted to them to drug control authorities throughout the world within specific time limits. Although legislation has strengthened the focus on the safety side of drug therapy, the procedures introduced have led to information overload in many regulatory offices and a great risk for case duplication in the international exchange of data. Resources would be much better spent if all so-called CIOMS I reports were submitted to 1 international database, set up according to the internationally agreed format and subjected to analysis with Bayesian neural network methodology.
- *Increase openness and trust between parties involved in drug safety assessment and communication.* The present restrictions imposed on dissemination of information from the WHO database are impeding the optimal use of the collected data. All interested parties, including industry, health professionals, media, academia, consumer groups, lawyers, etc, need to be properly informed about how to use information emanating from spontaneous ADR reporting in a scientifically sound way. Unrestricted access to information used as a basis for action and advice is likely to increase general understanding, the standard of the scientific discussion and respect for conclusions reached.
- *Attract resources for signal analysis and follow-up.* The total public spending on maintenance of the global system for collaboration in drug safety monitoring is negligible. As described in section 2.1, analysis of potential international drug problems are, today, largely dependant on voluntary efforts by international experts. Funds to support follow-up studies of identified problems are presently unavailable. Ideally, an international expert panel could be established, mediating over certain research funds, which could analyse signals of potential problems coming out of the WHO database, make priorities as to which signals warrant further investigation and suggest suitable approaches and databases to use for the analysis.
- *Pro-active analysis of the WHO database to assist in the development of safer drugs.* Pharmacovigilance is a part of preventive medicine. The aim is to learn as much as possible from past experience to avoid drug-related injuries among future patients. Thorough analysis of the big WHO database enables studies of relationships between chemical characteristics of drugs, e.g. their structures, and their adverse effects, as reported from clinical practice. Such knowledge should be useful in the design of safer future medicines.

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