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WORLD HEALTH ORGANIZATION
ORGANISATION MONDIALE DE LA SANTE

REPORT OF THE EIGHTEENTH ANNUAL MEETING
OF NATIONAL CENTRES PARTICIPATING IN THE
WHO INTERNATIONAL DRUG MONITORING PROGRAMME

BANGKOK, THAILAND

4-7 DECEMBER 1995

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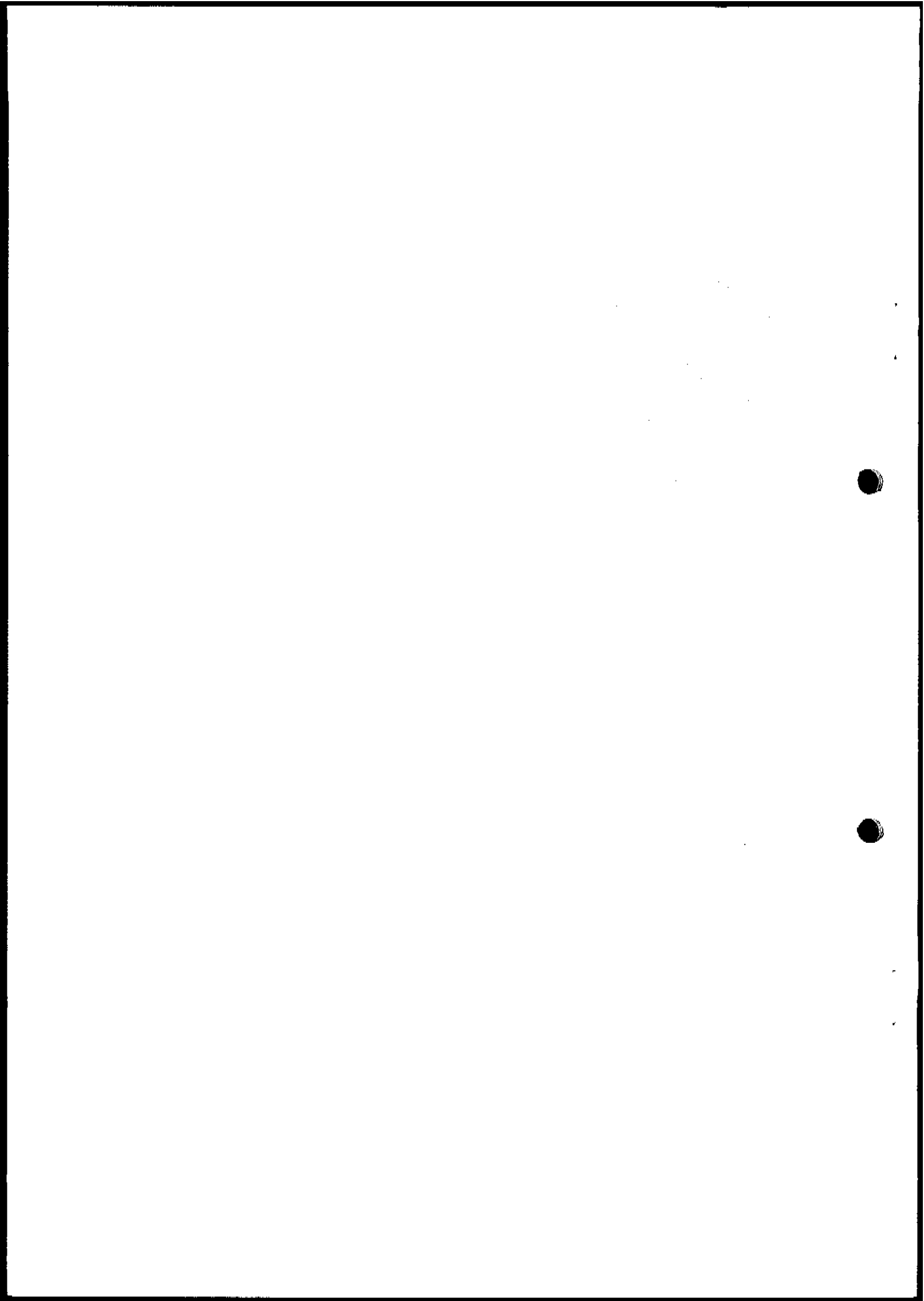


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1. Opening of the Annual Meeting

The meeting was formally opened by his excellency Mr. Sanoh Thienthong, Minister of Public Health. He welcomed the international and national participants to the meeting and acknowledged the WHO and member countries for their efforts to ensure the safety of drugs globally. He stated that sharing and exchanging knowledge and experiences contributes to the success in ADR monitoring.

The welcome address was delivered by Dr. Vitura Sangsingkao, Permanent Secretary of Health. Prof. Dr. Pakdee Pothisiri, Secretary General of the Food and Drugs Administration, on behalf of the organising committee expressed his appreciation to the Minister of Public Health for gracing this opening and provided a background on ADR monitoring in Thailand. He stated the objectives for this meeting, such as finding solutions to address the problems and issues of ADR, exchanging experiences among countries in ADR monitoring and enhancing the technical knowledge of persons involved in this area of work.

Dr. Martijn ten Ham, head of WHO Drug Safety Unit, on behalf of Dr. Hiroshi Nakajima, the Director-General of the World Health Organization, welcomed the participants to this meeting. He cited the many WHO programmes where Thailand plays a major role, one of which is ADR monitoring since their membership in 1983. He expressed his appreciation to the Thailand authorities for graciously hosting this meeting.

(Full texts of these introductory statements are attached in annex A)

2. Nomination of Officials

Dr Pakdee Pothisiri accepted to be President of the meeting. Mr. Bruce Hugman (Equus, communications consultant for WHO Collaborating Centre for International Drug Monitoring) was elected facilitator of the meeting. Ms. Carol Bouchard (Canada) and Dr. Kenneth Hartigan-Go (Philippines) were elected rapporteurs.

3. Report from WHO

Dr. Martijn ten Ham, WHO Headquarters, gave a review of developments since the 17th Annual Meeting held in Berlin, Germany on 27-30 September 1994. He discussed three major issues and their current status. These issues in particular are: ADR terminologies, Counterfeit Drugs and Regional/National Developments. He discussed the decision made at a meeting sponsored by CIOMS in Washington, USA, September 1994, on the adoption of the UK system for ADR terminology (MEDDRA) and following the 17th Meeting of National Centre Representatives in Berlin 1994. Issues such as how this system will behave in practice and who will be responsible for maintaining such a system needs to be clarified. There was no opportunity before the Berlin meeting to investigate the actual application for the proposed system. The system had been made available during 1995 to National Centres for testing. However, very few reactions had been received from individual Centres. Discussions on the system, in particular on its maintenance, continue within the Conference of Harmonization (ICH). It has been proposed by ICH that an independent/semi-governmental organization be contracted to maintain and manage such a system. An "implementable" version of the terminology should be available by July 1996.

He further cited that counterfeit drugs represent a great hazard to public health. Estimates of the proportion of counterfeit drugs on the marketplace range from 5% in developed countries to 40-50% in developing countries. In the framework of a recently established WHO-project certain initiatives and practical steps are being taken to address the problems of counterfeit drugs. These include establishing analytical methods to investigate counterfeit drugs and initiating linkages with other organizations such as the International Customs Organization and the international police agencies. A country study will be conducted by the WHO Drug Action Programme in Geneva to obtain more detailed information on the situation at country level. Consultations have been held to identify simple analytical testing methods for suspected samples. In 1996 further consultations will be organized on the education of officials involved in the distribution chain, and on the implementation of suggested measures at country level. A global workshop is planned for the end of 1996.

There were many national/regional developments over the year. A meeting in Pakistan in January this year demonstrated fruitful results. In April, 1995, the first regional pharmacovigilance meeting was held in Buenos Aires with the view for networking different centres in South America. With the help of the Collaborating Centre Brazil is now in the process of establishing a national decentralized system. Discussions to strengthen Eastern European countries are under way.

Dr. I. Ralph Edwards, director of the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden gave his annual report (see Annex B). He cited the efforts of his staff in the centre including a study of the outcome of signals, a project being managed by Mrs. Helena Fucik. The efforts to introduce research strategies are currently managed by Ms. Marie Lindquist. Ms. Cecilia Biriell has been actively involved with ADR terminologies development and review. Mr. Sten Olsson has been actively preparing technical courses both regionally and nationally. A problematic area recognized is that of ADR from the use of herbal medicines, and Dr. Mohammed Farah is currently assisting the centre in this matter. Mr. Bruce Hugman has been appointed as a consultant to assist and improve the collaborating centre as well as national centres in matters relating to communications.

4. Working Groups

Four working groups were convened to address the problems of ADR terminologies, Communications, Output documents, and Causality assessment. Dr. Kampon Sriwatanakul (Thailand) and Mr. Bruce Hugman (WHO) acted as chairman and facilitator respectively for the presentation to the plenary meeting.

4.1 ADR Terminology (Annex C)

The working group was chaired by Dr Borvendeg, Hungary and Ms Marie Lindquist was the WHO-centre resource person. Dr. R. Pless (Canada), on behalf of the working group, presented their results of the discussions. He provided an introduction on the rationale for having an ADR terminology, which should be able to facilitate a clear coding system with multiple tiers and with provisions for future retrieval. It was appreciated that MEDDRA was chosen by the countries participating in ICH to be the system to be the basis for further development. MEDDRA originates from the UK adverse drug reactions terminology (ADROIT), and had been developed together with representation from the industry and the regulatory agencies of France and Spain. The working group cited some basic problems, such as identifying the

persons or groups to maintain the system and the projected costs to member countries who will be using the terminology.

The working group recommended that the WHO Collaborating centre be requested to approach the ICH expert working group for medical terminology and take the lead role for creating and maintaining a subset of terms specifically addressing issues of drug safety and pharmacovigilance.

4.2 Communications (Annex D)

Dr A. Wong, Brazil, acted as chairman and Ms Monica Pettersson was the WHO-centre resource person. Dr Wong presented the working group outputs. He cited that the present lines of communication between WHO and national centres are satisfactory. However, this could be expanded to include information from National Centres on early signals, suspected ADR:s, national bulletins, newsletters and publication. It was also proposed that there be regular exchange of information and be done with greater frequency with the advent of electronic formats (i.e. E-mail). The list of reviewers and consultants of WHO should be made known to the national centres (see enclosed list). The working group further proposed in relation to the WHO data base that

- Its use should be accessible to all inquirers, provided that
 - the CAVEAT document be followed
 - it is in the public health interest
 - relevant countries be informed that the search has been requested
- Access is available within two weeks, but should be more timely for emergencies

4.3 Output documents (Annex E)

Ms Niamh Arthur served as the chairperson and Mr Sten Olsson was the WHO-centre resource person. Ms Anne van Ermen, Belgium, presented the output of the small working group, in which Belgium, Canada, Ireland, Philippines and Sweden were represented. The list of yearly and quarterly output documents from WHO Collaborating Centre was reviewed. It was noted that although the volume of WHO publications is large they are of limited usefulness. A practical solution proposed to improve its usefulness is to a) have sufficient reviewers to assess them and b) to index these documents. It was further raised that the frequency of document distribution be reduced or could be provided only on demand. It may be necessary to redefine the criteria, the contents and the amount of information to be placed in the documents. The manner (layout) by which these documents are presented should be reviewed by experts in the field of communications. Furthermore, a questionnaire to solicit comments regarding the usefulness of the documents, and their application to education and training should be sent to national centres.

Global issues may not necessarily be national centre's concerns. To make the output document useful this must be taken into consideration. Collaboration with the Cochrance group is underway however, confidentiality issues need to be addressed when the time comes to use the WHO database. It was also evident from the participants that some national centres conduct mini-reviews of ADR cases that are not widely communicated to other national centres who nevertheless might be concerned with the same issues. As a consequence of this, the value of e-mail discussion groups was entertained.

Causality Assessment (Annex F)

Dr. R. Meyboom (Netherlands) chaired the meeting while Dr. P Duclos (Canada) served as rapporteur and Mrs. H. Fucik acted as resource person from the WHO Collaborating Centre. The objectives of this working group were to exchange views on 2 major issues: the need for causality assessment and how to assess causality.

Dr. P. Duclos presented the group's output. A definition of terms, in particular, adverse drug events and adverse reactions has been done by the WHO Programme. The different factors to consider when causality assessment is done were discussed. It appeared that causality assessment should be considered as a means and not an end. For cost-effectivity, it should be applied to serious cases.

The processes and problems for assessing causality were discussed, noting that they may be variable in different centres and that complete information is often lacking. It was pointed out that although many centres used the 6 WHO categories for causality assessment (certain, probable, possible, unlikely, unclassified and unclassifiable), they have different definitions for these terms. It was also proposed by the group that industry should never be represented in committees performing causality assessment.

The group recommended that in future training courses on ADR, it may merit covering causality assessment. Moreover, the methods by which causality assessment in each country are done should be documented so that review of the WHO database by other centres may be properly interpreted.

5. Drugs of Current Interest

The drugs of current interest list is found in Annex G. Participants from different countries presented their problem drugs.

Australia

The national centre of Australia presented two drugs associated with hepatic dysfunction, flucloxacillin and amoxicillin-clavulanic acid. This appeared to be duration and age-related effect with flucloxacillin and age-related effect with the other drug. A dose-related phenomenon was similarly observed in New Zealand. Another drug of interest on the rise is loratidine implicated to cause adverse cardiac reactions, similar to that seen with astemizole and terfenadine.

The National centre raised potential problems with dinoprostone. Reactions pertaining to uterine rupture and foetal distress (9 cases) were discussed. Cases of cardiac arrhythmia associated with erythromycin IV were also discussed. These cases appeared to be related with the infusion rate. An accelerated rate of infusion may cause more cardiac effects. The centre also brought up cases of lactic acidosis associated with metformin, in particular with high dose of approximately 3 gm/day. Cases of hepatotoxicity associated with the use of coumarin were discussed. The centre received 12 cases last year one of which was fatal. The phenomena is difficult to explain which brings uncertainty in deciding a course of actions.

The presentation by the Australian centre stimulated discussions and the following points were raised. Dr. Feenstra from Holland pointed out that it is important how dinoprostone gel is applied. Ms Coulson from the UK reported 7 reports of cardiac arrhythmia associated with the use of erythromycin IV and that the product license has been changed. Dr. Stoller from Switzerland reported also 6 cases of hepatotoxicity associated with the use of coumarin and that they will reconsider the risk/benefit of this drug. Dr. Feenstra from Holland reported cases of hepatotoxicity from results of a study currently on-going and accepted to share more details on these results with participants when available.

Belgium

Reports on oral contraceptive (OC) and the risk for thromboembolic events have been observed. Although there are no published studies on these events, Dr. IR Edwards cited at least three on-going investigations looking into this issue. It appears that the so-called third-generation OC (containing gestodene or desogestrel as progestogens) are associated with an eight-fold risk of thromboembolic events as compared to non-users, whereas the old OC have a three-fold relative risk as compared to non-users. The new OC:s, however, may have a lower risk for myocardial infarction and cerebrovascular disease, though the numbers are not significant enough for making definitive conclusions. The data in the WHO data base regarding the new progesteron OC agents are still being investigated by signal analysis, but the trends are similar to the unpublished results from other studies. In the analysis of these studies, it was noted that many patient variables should be taken into considerations, in particular the lower frequency of prescribing of OC to patients in the light of family history of thromboembolism, however, these data are not available.

Belgium also raised the problem of herbal medicine. These popular drugs are often complex mixtures, the purity and contents of which are often unknown. A national system was recommended in order to obtain ADR reports from these preparations. Currently, there are 5,000 ADR reports following herbal medicine use in the WHO database. One of the problems observed was that many national centres do not actually ask for these reports and reports of these nature consequently get directed towards the poisons centres.

Brazil

Brazil has the second largest leprosy population in the world, second to India. Although the prescription of thalidomide requires the use of special yellow prescription sheet, it appears that this drug may be available in the streets. The ADR associated with the use of thalidomide is well known, in fact it is one of the reasons why international ADR monitoring started. Largely, the ADR of this drug is caused by ignorance and/or the neglect by physicians to warn and inform their pregnant patients. There were 50 new cases of phocomelia in Brazil in the last 15 years. There is also a fear that more cases may be seen particularly since thalidomide is now being used illegally as a street drug for the treatment of AIDS.

Canada

Three cases of nicotine patches causing nicotine toxicity during vigorous activities following single dermal application were reported. The manifestations included euphoria, nausea, vomiting, disorientation, tremors, dizziness, hives on the face, extremities, chest, palpitations, severe fatigue, insomnia and acute myocardial infarction. It was found that the product information regarding use during exercise was not

available. Following these events, an ADR newsletter warning against the use of nicotine patches during exercise was published citing that the mechanism might be increased absorption during strenuous activities specially in high risk patients with history of smoking.

The national centre presented a summary of 12 cases of hepato-biliary reactions associated with the use of terbinafine. The Canadian product monograph has been now changed to reflect that there is possibility of occurrence for this type of reactions. Information on this matter will be sent to health professionals in the near future. The problem of taste lost or taste disturbances with terbinafine was also discussed by other countries.

The National centre in France presented information on terbinafine. Cases of blood disorders and hepatic abnormalities have also been reported which led them to take actions such as informing prescribers and modifying the product monograph. The UK has also changed the data sheet for terbinafine. They reported cases of hepato-biliary reactions in which they had one fatal case. Dr. Mathias from Germany mentioned that they have received over 300 reports. The most frequent reactions reported are related to taste but they also have cases associated with hepatic dysfunction. The total number of cases presented by various countries seems important in comparison with the ones currently residing in the WHO database (184 cases). The group concluded that perhaps many reports have not been submitted yet. Dr Coulter from New Zealand mentioned that terbinafine profile was examined a few years ago and at that time, it had already appeared that there were potential problems with this drug.

France

Sparfloxacin (Zagram 200 mg) has been reported to cause photosensitivity following intensive post-marketing surveillance of this new agent. The steps taken by France to ensure the safety of use following this signal were presented. Other relevant ADR:s following the use of sparfloxacin included prolonged QT intervals, tendon disorders, anaphylactic reactions, neuropsychiatric disturbances, thrombocytopenia and photomutagenicity. These reports are relatively new and have not yet been reported to the WHO Collaborating Centre.

Germany

Fluoroquinolones have been implicated in the causation of suicides and depression. Between 1977-1995 there were 73 cases of depression and 22 cases of suicides or attempted suicides. The mechanism for these is unknown but apparently, they may appear suddenly and early in the course of treatment. The results will be published.

Hungary

Clavulanic acid component of some antimicrobials has been implicated to cause allergic skin reactions. Initially the reaction was thought to be due to the beta-lactam antimicrobial however recent evidence (dechallenge and rechallenge) has shown that clavulanic acid may be the aetiology of the ADR. If the figures of ADR were examined, since 1972 to date, there are 885 ADR reports from an estimated 450 million takers of amoxicillin however with the introduction of Augmentin since 1981, there are 2220 reports of ADR from an estimated 375 million takers.

Morocco

Two cases of azithromycin associated with Kawasaki syndrome were presented. This occurred in the paediatric age group (10-11 year old). The adverse reactions included fever, skin eruption and exfoliation, cheilitis, conjunctivitis, elevation of liver transaminase enzymes and hyperleucocytosis.

Netherlands

Alfuzocine (an alpha-1 blocker) used for the treatment of benign prostatic hypertrophy has been reported to cause myocardial infarction, angina pectoris and hypotension. Warnings will be proposed to ensure the safe use of this agent.

A case report of interstitial pneumonitis associated with the use of nabumetone was presented. Dr. Velo from Italy suggested that the risk/benefit ratio of this drug should be considered and that other drugs can be used instead. It was also brought up that the amplitude of side effects can be associated with the amount of dose administered which can eventually mislead interpretation.

New Zealand

There were a number of drugs of current interest from New Zealand. In order to understand the listing, an introduction of the Intensive Medicines Monitoring Programme was presented. The New Zealand system includes both prescription event monitoring and spontaneous monitoring. Following an analysis of these two systems, it was found that the rates of reporting differ widely.

Omeprazole associated with polymyositis was reported in three cases recently. When compared to other drugs the relative risk was 2.3. A similar phenomenon to this reaction was observed in Netherlands and a report (with elevation of CPK enzymes) was also reported in the literature.

Singapore

From 1993 to date, there were 1255 ADR reports (population 3 million). Fifteen (15) ADR reports received by ADR monitoring unit were due to vaccines.

Thailand

Data on the malaria mortality rate in Thailand from 1949 to 1993 were presented. The rate has decreased consistently showing a certain success in the activities undertaken. The Post Registration Surveillance of the safety of artesunate and artemether, two antimalarial drugs, was explained by presenting to participants the objectives, methodology and approaches as well as on how the drugs are distributed and used. The impacts of this surveillance were also described and a current status on the number of ADR reports presented.

6. Communication Techniques

Mr. B. Hugman (EQUUS), the external consultant for the WHO Collaborating Centre, explained the importance of proper communications. Most communications are about processes, and when applied properly, will influence readers. He cited that improvements of existing WHO manuals and documents are in development. There is also the intention to help national centres to develop low budget but effective communication materials to improve ADR reporting (i.e. ADR forms) and promote drug safety.

7. ADR signals

Dr. IR Edwards briefly presented the important role that signals play and introduce the evaluation process and results of the ADR Signals Analysis Project (ASAP). He cited that because of the massive data accumulated by WHO, outputs in different matrices may be generated depending on the requests made by national centres. He presented another project called the Automated Signal Review. This project is in the early stage of development whereby problems in clusters can be automatically produced through the utilization of computers and neural networks. The rationale for this system is based upon the premise that with more ADR cases reported, the association to drugs becomes more likely.

8. CIOMS activities

Dr Martijn ten Ham gave a brief history of the CIOMS. This organization had been created in a joint effort of UNESCO and WHO, but emphasis of its activities has been shifted to the area of WHO effort. CIOMS works in close cooperation with WHO which has been represented in the various working groups held on the following topics : CIOMS - 1 reporting form, CIOMS-2 periodic safety data, CIOMS-3 core data sheet and CIOMS-4 benefit/risk of drugs (currently on going). Dr. Martijn Ten Ham on behalf of the secretary general, Dr. Bankowski, reported on activities undertaken on the harmonization of terminology relevant to drug safety. It was proposed by Ms. Astrup from Denmark to provide participants with a copy of Dr. Bankowski's paper.

Dr. Ralph Edwards presented information on the CIOMS 1-A working group which concerned the electronic reporting format for industry. Since its origin in 1986-1987, CIOMS-1 contributed to a worldwide increase in the number of reports which subsequently resulted in severe logistic problems in handling large numbers of such reports and a professional/ethical problem if they are ignored. The two options considered were to either change the CIOMS-1 and WHO formats to adapt to a single required format or to create a parallel WHO database for industry.

Dr. Edwards also pointed out that the European Union with the International Conference on Harmonization (ICH) worked for a similar objective in relation to a common electronic reporting format to transmit information from all sources. The electronic reporting format of the CIOMS 1-A working group is very similar as the one developed by ICH and Dr. Edwards presented the various elements of this format. During the review, emphasis was made on data fields that are very important particularly if the option of creating a parallel database is adopted. Dr Edwards emphasized that a parallel database for industry requires capability to perform audit trail.

A comparison between the number of adverse Drug reaction reports contained in an industry database and the ones contained in the WHO database was presented. From results of this comparison, it appears that not all reports are provided to WHO. Dr. Edwards mentioned that this is not satisfactory. National regulatory agencies are expected to forward all reports to WHO and logically the data base should contain all information.

Dr. Martijn ten Ham brought up the issue of potential differences in reporting because of variances in legal requirements for manufacturers reporting. Dr. Chen from USA explained 2 types of approaches taken in public health which are to restrict variables of interest for some drugs and enlarge it for others when needed. Dr. Robert Pless from Canada agreed to coordinate a group of participants who are interested to discuss the issue. The topic will also be addressed by the working group on communication.

9. Advisory Group

Mr Sten Olsson, General Manager of the WHO Collaborative centre explained the objectives of the advisory group and gave a status of the present situation. He raised the issue of expanding the Centre's administrative board to include, on rotational basis, one representative from the National Centres. The issue generated many questions from the participants with regard to the current members composition, the cost of bringing a member from a National Centre, the length of terms, the Board functions, the frequency of meetings, the pertinence of this initiative and the difficulty for the representative to conciliate opinion of all centres.

It was formally proposed by Dr. Beckmann (Germany) to eliminate the advisory group and instead add a permanent position representing the National Centres to the administrative board of the WHO-centre. Dr. Chen (USA) suggested that regular communication with National Centres may be a satisfactory substitute for the proposal made. It was also proposed to schedule time at the annual meeting to review administrative topics.

Participants were invited to identify their interest in this issue to Mr. Olsson or to provide their comments in writing

10. Vaccine associated Adverse Events Reporting (Annex H)

The purpose of this session was to highlight the unique requirements and challenges inherent in vaccine-associated adverse event monitoring. The intention of this session is to allow national centres to improve surveillance of vaccine associated adverse events and therefore enhance global Drug safety. The session was opened by Dr. P. Duclos (Canada). It was noted that there is a low rate of ADR reporting following vaccine use and that variation exists in reporting rates over time and when comparisons were made in terms of proportion within the ADR database worldwide.

USA

Dr. R. Chen (CDC, USA) cited the role played by the Centre for Disease Control in the assessment of vaccine safety used in the United States. Vaccines are Drugs used across all populations to prevent

illness. He presented various methods minimizing the injuries due to vaccines such as developing safer vaccines or eradicating the disease (e.g. small pox). One of the gaps noted was the insufficient knowledge about diseases and their biological processes. Two ways that may be applied to detect problem vaccines are passive and active surveillance. Examples of passive surveillance include the detection of recent adverse events where previously not reported and the co-operation with the US Food and Drugs Administration by performing quality assurance. Active surveillance includes the validation of signals, the identification of risk factors and communicating these risks to appropriated agencies and parties. According to US legislations, there is a 30 day criteria for reporting vaccine adverse events which is presently considered short, as in many cases, adverse events may still occur around and beyond 6 weeks post immunization. It was proposed that reporting be left to the clinician's discretion.

Canada

Dr. R. Pless outlined the use of vaccines within the framework of the Canadian health care system. He proposed that the generation of signals from vaccine adverse events be linked to disease surveillance and tracking and case reporting. There was a steady increase in reporting since 1987 as a result of constant feedback. There are presently other systems which contribute to the success of reporting, in particular, the institutionalization of active paediatric hospital surveillance and the use of expert advisory committee to review serious cases.

Thailand

Dr. Kampon Sriwatanakul reported that since 1983, the national adverse Drug reactions centre, linked to 19 regional centres, numerous general hospitals and community centres has been collecting vaccine associated adverse events. He cited the frequency counts of these cases between 1984-94. As a result of these reports, one of the positive actions taken was to remove problem vaccines from the market with the view for ensuring Drug safety. The feasibility of phase III/IV studies toward HIV vaccines should be considered.

World Health Organization-Expanded Programme on Immunization

Dr. J. Milstein cited the different characteristics of Adverse Events following Immunization (AEFI) that may be used as indices of programme quality and credibility and may be used to strengthen the programme. Clearly, there are three types of AEFI. These are programme-related, vaccine-induced and coincidental. Examples of programme related events are those problems associated with administration, storage, transport, reconstitution, incorrect preparation and sterilization. Examples of vaccine related events are those specific to the batch and lot of a particular product. Examples of coincidental events are those mislabelled as adverse Drug events but actually a consequence of certain patient risk factors (i.e. disease). When there are deaths due to vaccine administration, huge negative impact is created in the locality of the programme. When programmatic errors occur, practical steps to consider during investigations include details of the patients, events, common practice in storage, handling, administration, and the number of people immunized and affected by the same vial of vaccines. Experience has demonstrated that documentations and feedback are necessary part of immediate action by the investigator. The programme will circulate a field guide for AEFI surveillance made available two years ago, prepare an investigation checklist and an inventory of the appropriate laboratories and promotion of safe injections.

Germany

Dr. M. Fuchs introduced Paul-Ehrlich-Institute, also known as the National Control Authority for Sera, Blood products, vaccines and related immunological Drugs. This institute is responsible for licensing, batch control and release and performing basic research. There were 1500 ADR reports following vaccine use and a permanent vaccine commission was created to look into vaccine-related adverse reactions. A large proportion of cases manifest as neurological ADR and as a consequence, case definitions for neurological ADR were developed in co-operation with neurologists. He cited 3 existing problems, that medical doctors reporting these ADR:s are not required to document the batch number of the vaccines, there is gross under-reporting and that causality assessment is difficult.

There were a number of issues discussed. Concerning batch number and pertinent recording, in the US, a law passed in 1986 required all doctors administering vaccine to keep a logbook record for the purposes of retrospective investigation. The FDA Medwatch form was not found to be adequate for vaccine related ADR reports and therefore a separate system was deemed necessary.

Similarly in other countries, vaccine related ADR monitoring was proposed to be separate from existing drug monitoring system because the latter has many confounding variables making it difficult to pick up signals. An area for improved collaboration could be a standard protocol to be provided to medical doctors in order to harmonize the cases collected. Although it is difficult to obtain a control group for studies on vaccines, a definition of specific ADR terms following vaccine administration was proposed. As a practical and concrete measure to continue vaccine related adverse event monitoring, it was also proposed that discussion groups of this nature be conducted during international, national and local ADR meetings.

Issues inherent to the use of vaccine-related adverse events are summarized as follows: vaccines are given to healthy persons, when adverse events develop the causality assessment is difficult, and often a specialist is needed. There is also the problem of cocktail vaccines. The importance on programmatic errors is emphasized. The proposals and recommendations include having regular discussion sessions on vaccine-related adverse events in international and national meetings, having a list of people interested in vaccine ADR and the need for better communication with people working in this field. A discussion group on the INTERNET was proposed. For countries with new vaccine programme, to include ADR monitoring as part of disease surveillance or immunization programme and to encourage the submission of these reports to WHO Collaborating Centre. Following this, to also look at how information on vaccine-related ADR cases are kept in the WHO database. There is a necessity to improve clinical trials for vaccines by exchanging information between Drug and immunization programmes.

11. Computer sessions

Two short computer sessions were prepared attended by 14 participants. The areas covered were a demonstration of online searches in the WHO database and searches in the Drug dictionary. The sessions were co-ordinated by Marie Lindquist.

12. Comments/Recommendations/Summary

Communications

A common issue with regards communication is that an INTERNET discussion groups be created to facilitate continuation of information exchange.

ADR terminology

A detailed resolution of this group can be found in Annex C.

ADR Signals

National Centres were requested to share information about early ADR signals with colleagues in other Centres.

Advisory Body

Instead of convening meetings with an Advisory Group the WHO-centre should keep National Centres better informed of issues dealt with by the administrative board, possibly through the Newsletter.

Output documents

Recommendations of the relevant working group are given in Annex E.

Causality Assessment

Considerations and recommendations of the working group dealing with this issue are given as Annex F.

Vaccines-related adverse event monitoring

Conclusions and recommendations of this session are provided separately as Annex H.

13. NEXT ANNUAL MEETING

The next annual meeting of National Centres participating in the WHO International Drug Monitoring Programme will be in Lisbon, Portugal from September 16 to 18, 1996 inclusive. The meeting will be followed by the annual meeting of the European Society of Pharmacovigilance which will last until September 20, 1996. The next annual meeting will be hosted by the National Institute of Pharmacy and Medicine.

14. Other matters

It was suggested that considerations to devote more time to developing countries' issues be made. Pakistan requested for access to National Centre newsletters and WHO Collaborating Centre was asked to facilitate this (see recommendations).

15. Closing Ceremony

Mr. B. Hugman, facilitator of the meeting, first thanked the participants and noting their excellent and productive outputs. He then, on behalf of WHO and the participants, gave a vote of thanks to the Thai team for their exceptional, kind, rich hospitality.

Dr. Martijn ten Ham highlighted that this is the first annual meeting of national centres held in Asia and appreciated the support that the Ministry of Health provided for this meeting as well as the programme on ADR monitoring. He noted that the different working groups gave good recommendations and encouraged all participants to take active role in the implementation of these recommendations. On behalf of the WHO, the participants, he gave his deep appreciation to Ms. Suboonya and her staff, Mr. B. Hugman, chairman and facilitator for a professional meeting, the WHO Collaborating Centre for their technical and professional support, and Dr. K. Hartigan-Go and Ms. Carol Bouchard for their efficient assistance as rapporteurs of this meeting.

Dr. Kampon, on behalf of the Food and Drugs Administration Secretary General Prof. Dr. Pakdee Pothisiri and the ADR monitoring unit of Thailand, thanked the chairman and rapporteurs, Dr. M. ten Ham, the international and local organizing committee for their assistance. He wished the participants a safe trip home.

Annex A: Inaugural speeches

Annex B: Annual Report of the WHO Collaborating Centre

Annex C: Request for the WHO Collaborating Centre from the participants of the 18:th National Centres Meeting regarding ADR terminologies

Annex D: Working Group on Communications

Annex E: Working Group on Output documents

Annex F: Working Group on Causality Determination

**Annex G:
Drugs of Current Interest List**

**Annex H:
Conclusions and recommendations from session on vaccine-associated adverse events**



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Annual Meeting of the WHO International Drug Monitoring Programme Bangkok, 1995

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REVIEWERS - SOCs

November 1995

Reviewer	SOC	SOC nr
Dr Wybo Bruinsma	Application site	1820
	Skin & Appendages	0100
Prof Rick Day	Collagen	0300
Dr Toine Egberts	Central Nervous System	0410
Prof Fritz Fraunfelder	Vision	0431
Dr Lennart Lundin	Cardiovascular	1010
	Heart rate & rythm	1030
	Myo-, endo-, pericardial	1020
Dr Laurie Mashford	Critical terms list	
Dr Ronnie Meyboom	Platelet, bleeding & clotting	1230
	Red blood cell	1210
	White cell & RES	1220
Dr Florabel Mullick	Critical terms list	
Dr Ed Napke	Psychiatric	0500
	Resistance mechanism	1830
	Respiratory	1100
Prof Ralph Edwards	Central Nervous System	0410
	Neoplasms	1700
	Secondary Terms	2000
	Signal follow-up document	
	Vascular	1040
	Reproductive, male	1410
	Urinary system	1300
	Endocrine	0900
	Metabolic	0800
Dr Eugène van Puijenbroek	Endocrine	0900
	Metabolic	0800
Dr Franz Rosa	Foetal	1500
	Neonatal	1600
	P-report (foetal)	
Prof René-Jean Royer	Musculo-skeletal	0200
Dr Ruth Savage	Reproductive, female	1420
Dr Bruno Stricker	Gastro-intestinal	0600
	Liver & biliary	0700
Prof Giampaolo Velo	Body as a whole	1810
	Hearing & vestibular	0432
	Special senses	0433
Prof Bodizar Vrhovac	Cardiovascular	1010
	Heart rate & rythm	1030
	Myo-, endo-, pericardial	1020

Report by Secretary General of Food and Drug Administration, Prof Pakdee Pothisiri

Excellency, Representatives from the WHO Headquarters and the WHO Collaborating Centre for International Drug Monitoring, Distinguished Participants, Ladies and Gentlemen,

On behalf of the Organizing Committee of the 18th Annual Meeting of National Centres Participating in the WHO Programme on International Drug Monitoring, I would like to express my sincere thanks and appreciation to Your Excellency, the Minister of Public Health for kindly spare your precious time to preside over the opening ceremony of this meeting which Thailand is greatly honoured to host.

May I be allowed to take this opportunity to report to Your Excellency the background and objectives of the meeting as follows:

Dating back in 1962, there was a tragic incident due to Thalidomide. A great number of phocomelic infants were born from mothers using Thalidomide during pregnancy between 1957-1962. At the same time, numerous cases with mild and severe adverse drug reactions had also been found. It was considered high risks to the people if the drug had been distributed without post marketing monitoring. Following this event the World Health Organization and the developed countries launched a national adverse drug reaction monitoring programme in order to collect and analyse information concerning adverse drug reactions and other relevant data of harmful effects of drugs such as death, cancer etc. The circulation and exchange of the information has been a great asset to the authorities concerned to take prompt action on drug consumer protection. The WHO Collaborating Centre for International Drug Monitoring located in Uppsala in Sweden was established almost 30 years ago. There are currently around 40 member countries including Thailand which became the 26th member in 1983. It is apparent that after the implementation of the drug monitoring system, drugs which may have harmful effects are withdrawn from the market as soon as they have been reported to the responsible authorities.

This meeting has been organized by the World Health Organization in collaboration with the member countries on an annual basis with the following objectives:

1. To consider problems with regard to adverse drug reaction monitoring;
2. To present country reports on the adverse drug reaction monitoring;
3. To exchange and share views, experiences and problems in adverse drug reaction monitoring among the member countries;
4. To enhance knowledge of personnel involved in drug and adverse drug reaction monitoring on technical aspect.

The three-day meeting from 4 to 6 December 1995 will include lectures, discussion, reports on adverse drug reaction monitoring and poster presentation. The meeting is attended by approximately 100 participants consisting of representatives from national adverse drug reaction monitoring centres of the member countries from all regions namely America, Europe, Africa, Australia and Asia, representatives from the World Health Organization, international agencies involved and 19 national adverse drug reaction monitoring networking centres of Thailand. The meeting has been organized with the support of several agencies both the government and private sectors namely Food and Drug Administration, International Health Division of Ministry of Public Health, Government Pharmaceutical Organization, Faculties of Medicine, Faculties of Pharmaceutical and Faculties of Science of Mahidol University and Chulalongkorn University, Pharmaceutical Producers Association and Thai Pharmaceutical Manufacturers Association.

Now it is the appropriate time, may I request Your Excellency to kindly deliver an inaugural address to the meeting.

Inaugural Address by H.E. Mr Sanoh Thienthong, Minister of Public Health

The Secretary General of Food and Drug Administration, The Representatives from the WHO Headquarters and the WHO Collaborating Centre for International Drug Monitoring, Distinguished Participants, ladies and gentlemen,

It gives me a great honour and pleasure to preside over the opening ceremony of the 18th Annual Meeting of National Centres Participating in the WHO Programme on International Drug Monitoring.

From the report of the Secretary General of the Food and Drug Administration on the background and objectives of the meeting, it is evident that the World Health Organization and its member countries have made a joint effort in the implementation of the drug consumer protection programme to ensure the safe use of drugs for people all over the world. On behalf of the Ministry of Public Health of Thailand, I wholeheartedly welcome all distinguished participants who have extensive knowledge and experiences in adverse drug reaction monitoring from various countries to our country.

I have noted with much appreciation that many internationally renowned experts from the World Health Organization and various countries have kindly participated in this meeting as speakers and panelists in discussion on specific issues which are of current interest and considerably beneficial to the public. I am sure that all of you will share and exchange knowledge, experiences and views in the area of ADR which will contribute towards the success of your work in drug monitoring. We, the Ministry of Public Health of Thailand are proud and pleased to take part in this challenging activity. As a host country of this meeting, I wish to ensure you that our health team, especially the Food and Drug Administration staff is most willing to provide to all of you any assistance and all possible facilities to make your stay here in Thailand a pleasant and enjoyable one.

With great pleasure, I now declare open the 18th Annual Meeting of National Centres Participating in the WHO Programme on International Drug Monitoring. May I wish the meeting every success and all the participants happiness and prosperity.

Welcome address from WHO

(Dr Martijn ten Ham, Chief, Drug Safety, WHO, Geneva)

Yours Excellency, Mr Permanent Secretary, Mr Secretary-General of the Food and Drug Organization, Colleagues and friends, ladies and gentlemen,

It is my great pleasure to welcome you on behalf of Dr Hiroshi Nakajima, Director General of the World Health Organization, on the occasion of the 18th meeting of National Centres participating in the WHO's Programme on International Drug Monitoring.

Why is it that Thailand is the venue for the meeting?

- Not because it is the oldest kingdom in the world,
- not because it is a country of outstanding exotic beauty (which it is)
- not because the Thai people are lovely (which they are)

but because of long standing contacts and cooperation between WHO and Thailand, particularly in drug monitoring.

To give two examples:

Thailand became member of the Programme as early as 1983. The WHO has been assisting in monitoring the introduction of the antimalarial artesunate. We are also happy to have the meeting in Thailand because we believe that we can learn. Adverse drug reaction monitoring in a tropical country may provide information on drugs used for tropical diseases. Although gradually disappearing, differences between highly industrialized and less industrialized countries still exist. Cultural, nutritional and health differences may influence patients reactions to drugs.

Through this meeting, we hope to achieve a better understanding of the specific problems a country such as Thailand faces. We hope that the Thai national programme on drug monitoring will benefit from our meeting. Participants at the Annual Meeting of National Centres participating in WHO's Programme on International Drug Monitoring will be welcome to attend, and more importantly, to contribute to the National Symposium on Thursday and Friday of this week.

Your excellency, Mr Secretary-General, we are very pleased with your interest in this meeting. It can only be interpreted as recognition for the programme Mrs Suboonya Hutangkabodee is running so aptly. We are grateful for the support to the work which the team of the National Centre carries out, and we hope that this meeting will contribute to the further development of this important work.

Once again, I thank the Government of Thailand for their generous offer to host this meeting and also thank other contributing parties for this opportunity to promote and bring together experts from many countries. Through the exchange of experience and information, we will all learn more about drug safety and come to a better understanding of safer medical treatment.

Thank you.



Report from the WHO Collaborating Centre for International Drug Monitoring

Activities July 1994 - June 1995

1. Introduction

The activities of the Centre are based on an agreement from 1978 between the World Health Organization and the Swedish Government. A foundation formed by the Swedish government is responsible for the administration of the Centre. The foundation is headed by a board of three members with personal deputies. Chairman of the board during the period was professor Kjell Strandberg. The other members were professor Folke Sjöqvist and Ms Birgitta Bratthall. WHO Headquarters was represented on the board by one observer.

2. Staffing

Director of the Centre is professor Ralph Edwards. At the end of the period the remaining staff consisted of 6 pharmacists, 2 secretaries and a manager of dictionary services. The internal management group was composed of professor Edwards, Ms Cecilia Biriell, Science and Quality Assurance Manager, Ms Marie Lindquist, Research and Development Manager and Mr Sten Olsson, General Manager.

3. New member countries

Argentina, Cuba, the Philippines and Venezuela were admitted as new member countries during the period, adding the total number of active participants to 45. Iran and Sri Lanka formally applied for membership. Eight countries are now awaiting full membership status while the issue of technical compatibility of their reports with the WHO reporting requirements is established.

4. Adverse reaction reporting

July 1994 to June 1995, 153 868 adverse reaction case reports were added to the data base of the WHO programme. The data base was updated on a weekly basis. By the end of the period the INTDIS data base contained 1.47 million case reports.

5. Feed-back of information to National Centres

5.1 Quarterly documents

Case reports submitted to the Centre were screened every three months to form the basis for different signalling documents. To remedy the problem of delayed distribution of signalling documents to National Centres the Collaborating Centre began printing and distributing routine output documents as of August 1994. By this change in routines National Centres will

receive the signalling documents several months earlier after production than before. Since early 1995 all National Centres also receive the quarterly documents, the WHO Drug Dictionary and WHO Adverse Reaction Terminology on diskette.

5.2 Annual documents

The reference document Report Type-A, containing summary figures on all suspected drug reactions reported to WHO 1988-94, was distributed as a three-volume document to all National Centres in early July 1995. Because of the large volume and limited edition of this reference book it has not been possible to have it printed at WHO Headquarters the last few years. It was now for the first time produced in its entirety and distributed from the Uppsala centre.

The 1994 edition of the WHO Drug Reference List, also printed in three volumes with more than 1300 pages, was distributed to National Centres in early 1995.

5.3 Adverse Reaction Newsletter

The Centre's Adverse Reaction Newsletter was produced and distributed in September 1994 and in January, March and June 1995. The Newsletter is based on communications, including national Adverse Reaction Bulletins, provided by the participating countries. Relevant communications on the electronic conferencing system DISNET are also included in the Newsletter. National Centres were invited to submit a list of 10 persons each to whom the Newsletter may be distributed. As a result each edition expanded from around 100 copies to 250.

5.4 On-line services

The number of National Centres having access to computers and electronic communication facilities is growing. As a consequence the number of users of the on-line search programmes provided by the WHO-centre continuously increase. At the end of the period 67 individuals from 31 countries had passwords to the INTDIS data base and the DISNET electronic conferencing system. The on-line service was provided free of charge for 3 users per country.

5.5 Ad hoc retrievals for National Centres

Although many National Centres now have on-line access to the INTDIS data base a substantial number of requests for ad hoc investigations are still received at the WHO-centre. The investigations requested are often of such a complexity that they cannot be managed using the on-line retrieval programme. July 94 - June 95, ninety one search requests from 27 programme member countries + WHO were processed.

5.6 Analysis of adverse reaction signals

The panel of reviewers engaged by the WHO-centre to assist with the analysis of new adverse reaction signals was expanded. Panel members not directly connected to any National Centre were formally connected to the WHO-centre as consultants. Four new reviewers were recruited to the panel in 94/95.

During the period 5 issues of the SIGNAL-document were distributed. Recipients were the same as for the Adverse Reaction Newsletter (see 5.3 above). In total 112 new drug-reaction associations were discussed in the reviews, the number increasing by 150% over the previous

year (Appendix 1). A questionnaire was distributed to recipients of the SIGNAL-document inquiring about the usefulness of the material. An analysis of the responses and the function of the signal analysis procedure was presented at the annual meeting of the Drug Information Association in Orlando, USA, June 1995 and will also be published (Appendix 3)

5.7 Evaluation of service provided to National Centres

A project was initiated to investigate the service level of the WHO-centre as perceived by National Centres. The communications consultant company Equus was employed to carry out interviews with representatives of selected National Centres. The project is aiming at improving the quality and specificity of information released from the Centre.

6. Support to development of National Centres

A two week training course on Adverse Reactions and Adverse Reaction Monitoring was held in May 1995 in collaboration with the Swedish National Centre. The course was primarily designed to provide basic knowledge and practical training for new staff members at National Centres and health professionals becoming involved in the establishment of new centres. Applications were received from 64 persons representing 45 different countries (Appendix 2). For reasons of efficacy of training, only 25 applicants could be admitted to the course, a majority of them coming from developing countries. Many of the participants received financial support from the Swedish aid organization BITS, the WHO Programme on Substance Abuse, WHO Regional Offices or the Nordic Council of Medicines.

A staff member of the WHO-centre was employed by the WHO Regional Office for the Eastern Mediterranean Region to investigate conditions and propose actions for setting up a national drug monitoring programme in Iran. The study was undertaken in December 1994.

In January 1995 the College of Physicians and Surgeons Pakistan organized a workshop on adverse drug reaction monitoring in Karachi, attended by a representative of WHO headquarters and one from the WHO-centre.

A conference on Pharmacovigilance in Latin America was organized in Buenos Aires, Argentina in April, 1995, by the Argentinean drug regulatory authority. The meeting was co-sponsored by WHO and was attended by representatives of 9 Latin American countries as well as officers from WHO headquarters and the WHO-collaborating centre. Subsequent to the Buenos Aires conference a shorter promotional activity was organized in São Paulo, Brazil.

The National Centre in South Africa and the emerging centres in Vietnam and Zimbabwe were visited by representatives of the WHO-centre during the period.

7. Release of adverse reaction information to external inquirers

The demand for information from the INTDIS data base from parties outside the WHO-programme is steadily increasing. The WHO-centre received and processed 151 search requests during the period, a 37 % increase from the previous year. The majority of requests came from investigators in the pharmaceutical industry but some also originated from academic researchers, consumer groups and clinicians.

The number of countries that accepts release of their data to any inquirer has increased to 27. Inquirers are asked to approach the remaining National Centres directly for permission to access data in the WHO data base.

On-line access to adverse reaction information from countries agreeing to general release of data is offered to interested third parties. Twelve pharmaceutical companies and one independent foundation were subscribing to this service at the end of the period. Before being granted access to the data base they have to guarantee that the conditions of the agreed Caveat Document will be complied with.

8. Development of the computer support systems

The WHO data base INTDIS is run in UNIX-environment on a computer located at the Uppsala University Computer Centre (UDAC). The data base management system was upgraded to a new version to allow for more efficient retrievals, using SQL language directly from the Centre's PC-network. The computer service company PharmaSoft Swedis AB was contracted to manage maintenance and development of the major data base. Another company, Coda Software HB, was employed to design customized programmes in PC environment for the Centre.

Development of new software was undertaken mainly to support management of requests for retrievals from the WHO-data base. A number of standardized data presentations have been developed. One presentation is consonant with the line listing proposed by the CIOMS II working group.

9 Terminologies

9.1 WHO Drug Dictionary

The drug products described in the WHO Drug Dictionary represent an ever increasing part of the international drug market. An increasing number of research based pharmaceutical companies and Contract Research Organizations (CRO:s), carrying out clinical trials on an international basis, subscribe to the Dictionary. A WHO Drug Dictionary Users Group, connected to the Drug Information Association (DIA), facilitates contacts between the WHO-centre and industry users.

One representative of the Centre continued to serve on the Advisory Board to the WHO Collaborating Centre for Drug Statistics Methodology, Oslo, Norway, with the main interest of developing the ATC-system for classification of medicines.

A project was initiated to refine the WHO Drug Dictionary to allow for e.g. the identification of pharmaceutical forms and strengths of product names included.

9.2 Adverse reaction terminology

The joint project for development of a new adverse reaction terminology based on the WHO and COSTART-terminologies, mentioned in last years' annual report, was interrupted because the MEDDRA-terminology, sponsored by the British Medicines Control Agency, was adopted as the basis of terminology development by a working party within the International Conference on Harmonization (ICH).

The WHO Adverse Reaction Terminology is however still being maintained and developed. The number of users outside the WHO Drug Monitoring Programme continues to increase.

9.3 Harmonization projects

The director of the Centre was closely involved in the deliberations of the CIOMS working parties. The result of the CIOMS III and CIOMS 1A projects were published in 1995;

- Guidelines for Preparing Core Clinical-Safety Information on Drugs, CIOMS, Geneva 1995
- Harmonization of data fields for electronic transmission of case-report information internationally, CIOMS, Geneva, 1995

The Centre is also represented on the CIOMS IV working party dealing with issues of risk/benefit evaluations.

The European Committee for Standardization (CEN) initiated a project on Terminology and Coding Systems for Drugs. Ms Marie Lindquist of the Centre was appointed member of the 5 person core team of the project. The work is expected to be completed by early 1996.

Prof Ralph Edwards was involved in the activities of two working parties of ICH, one on clinical drug safety and one on medical terminology.

10 **Research**

A research project was developed by the WHO-centre in conjunction with the chairman of the EU pharmacovigilance working group and researchers at the IMS-company, with the aim of improving methodology for analysis of international adverse reaction signals. IMS is the only available source of comparable international drug utilization statistics. Research funds for a two year project, starting late 1994, was granted by EU (Biomed). So far two studies have been completed (Appendix 3).

In another research project scientists at the Royal Institute of Technology, Stockholm, have been commissioned to develop a method based on Bayesian artificial neural networks to improve identification and analysis of signals from the WHO data base.

11. **Cooperation with other organizations**

11.1 European Union

The director of the Centre was a member of the European Pharmacovigilance Research Group, which is trying to develop better methods for European use for the study of drug safety. He served as a chairman of the working party for spontaneous adverse reaction reporting

11.2 International Programme on Chemical Safety (IPCS)

An international network for exchange of case data on poisoning is being established within the framework of IPCS. The WHO-centre has assisted this process by providing technical guidance and practical tools i.a. a software for recording of poisoning cases including a severity score (TOXSCORE). Approximately 20 poison information centres around the world take part in the pilot phase of this project, recording poisoning cases according to the TOXSCORE methodology. The WHO-centre will be involved in the compilation and analysis of the collected information.

11.3. International Society on Pharmacoepidemiology (ISPE)

At the annual meeting of ISPE in Stockholm, August 1994, the Centre organized a seminar on methods for signal generation.

12. Meeting of representatives of National Centres

The 17th annual meeting of representatives of National Centres was held in Berlin, Germany, 27 - 30 September 1994. Delegates from 33 programme member countries and 8 countries with observer status were present.

13 Publications

A list of publications emanating from the Centre during the period is appended (Appendix 3)

14 Presentations

Representatives of the Centre were invited to present the activities of the WHO Drug Monitoring Programme and related subjects at various meetings and conferences:

- Drug Information Association, Conference on Clinical Data Management, Basle, Switzerland, November 1994. (Lindquist)
- International Programme on Chemical Safety, Newcastle, Scotland, February , 1995 (Edwards, Lindquist)
- Drug Information Association, Conference on Clinical Data Management, Philadelphia, USA, March 1995. (Biriell)
- Nordic Association on Clinical Data Management, Stockholm, May 1995 (Lindquist)
- Meeting on Drug Dependence in a Nordic Perspective, Reykjavik, Iceland, June, 1995 (Biriell)
- Drug Information Association, Annual Meeting 1995, Orlando, USA, June 1995 (Fucik)

Issue	Drug name	Adverse Reactions
94-10	CLOZAPINE	LEUKAEMIA
94-10	GOSERELIN	NEUROPATHY PERIPHERAL
94-10	INTERFERON	HYPERTHYROIDISM
94-10	LEUPRORELIN	NEUROPATHY PERIPHERAL
94-10	LOVASTATIN	AMNESIA
94-10	PAROXETINE	EPISTAXIS
94-10	PAROXETINE	GRANULOCYTOPENIA
94-10	PAROXETINE	LEUCOPENIA
94-10	PAROXETINE	PANCYTOPENIA
94-10	PAROXETINE	PURPURA
94-10	PAROXETINE	THROMBOCYTOPENIA
94-10	PRAVASTATIN	AMNESIA
94-10	SIMVASTATIN	AMNESIA
94-12	AZITHROMYCIN	DEAFNESS
94-12	LAMOTRIGINE	CONFUSION
94-12	LOMEFLOXACIN	AGITATION
94-12	LOMEFLOXACIN	ANAPHYLACTOID REACTION
94-12	LOMEFLOXACIN	NERVOUSNESS
94-12	METHAZOLAMIDE	ANAEMIA APLASTIC
94-12	NABUMETONE	AGGRESSIVE REACTION
94-12	OXAPROZIN	DEATH
94-12	PACLITAXEL	SEPSIS
95-02	ACETYLCYSTEINE	GRANULOCYTOPENIA
95-02	ACITRETIN	MALFORMATIONS MULTIPLE
95-02	AMANTADINE	HEART MALFORMATION
95-02	AMFEPRAMONE	MYELOID DYSPLASIA
95-02	BUSERELIN	EPISTAXIS
95-02	BUSERELIN	FACE OEDEMA
95-02	BUSERELIN	GUM HYPERPLASIA
95-02	BUSERELIN	HAEMORRHAGE NOS
95-02	BUSERELIN	PURPURA
95-02	BUSERELIN	STOMATITIS ULCERATIVE
95-02	CAPTOPRIL	ANURIA
95-02	CARBAMAZEPINE	SPINA BIFIDA
95-02	CHLORMEZANONE	THROMBOCYTOPENIA
95-02	CLOMIFENE	PREGNANCY MULTIPLE
95-02	DOMPERIDONE	ANAEMIA HAEMOLYTIC
95-02	ENALAPRIL	MALFORMATION SKULL
95-02	FELBAMATE	ANENCEPHALY
95-02	FELBAMATE	MENTAL DEFICIENCY
95-02	FENTANYL	BRAIN DAMAGE CONGENITAL
95-02	FLUNITRAZEPAM	GRANULOCYTOPENIA
95-02	FLUOXETINE	TENDON DISORDER
95-02	GINKGO TREE LEAVES EXTRACT	THROMBOCYTOPENIA
95-02	GONADORELIN	EPISTAXIS
95-02	GONADORELIN	FACE OEDEMA
95-02	GONADORELIN	PURPURA
95-02	GOSERELIN	BLEEDING TIME INCREASED
95-02	GOSERELIN	COAGULATION TIME INCREASED
95-02	GOSERELIN	FACE OEDEMA
95-02	GOSERELIN	FIBRINOLYSIS INCREASED
95-02	GOSERELIN	GINGIVAL BLEEDING
95-02	GOSERELIN	HAEMORRHAGE NOS
95-02	GOSERELIN	PURPURA
95-02	GOSERELIN	STOMATITIS ULCERATIVE
95-02	INTERFERON	BRAIN DAMAGE CONGENITAL
95-02	ISOTRETINOIN	TENDON DISORDER
95-02	LEUPRORELIN	COAGULATION FACTOR DECREAS
95-02	LEUPRORELIN	COAGULATION TIME INCREASED
95-02	LEUPRORELIN	EPISTAXIS
95-02	LEUPRORELIN	FACE OEDEMA

Issue	Drug name	Adverse Reactions
95-02	LEUPRORELIN	FIBRINOGEN PLASMA DECREASED
95-02	LEUPRORELIN	FIBRINOLYSIS INCREASED
95-02	LEUPRORELIN	GINGIVAL BLEEDING
95-02	LEUPRORELIN	GINGIVITIS
95-02	LEUPRORELIN	GUM HYPERPLASIA
95-02	LEUPRORELIN	HAEMORRHAGE NOS
95-02	LEUPRORELIN	PROTHROMBIN DECREASED
95-02	LEUPRORELIN	PURPURA
95-02	LEUPRORELIN	STOMATITIS ULCERATIVE
95-02	LISINAPRIL	ANURIA
95-02	LOVASTATIN	TENDON DISORDER
95-02	MEBENDAZOLE	PURPURA
95-02	MENOTROPHIN	PREGNANCY MULTIPLE
95-02	METHOTREXATE	CLEFT PALATE
95-02	METHOTREXATE	HYDROCEPHALUS
95-02	METHOTREXATE	SPINA BIFIDA
95-02	MINOXIDIL	HEART MALFORMATION
95-02	MINOXIDIL	HYPERTRICHOSIS
95-02	NAFARELIN	BLEEDING TIME INCREASED
95-02	NAFARELIN	COAGULATION TIME INCREASED
95-02	NAFARELIN	EPISTAXIS
95-02	NAFARELIN	FACE OEDEMA
95-02	NAFARELIN	FIBRINOLYSIS INCREASED
95-02	NAFARELIN	GINGIVAL BLEEDING
95-02	NAFARELIN	GINGIVITIS
95-02	NAFARELIN	GUM HYPERPLASIA
95-02	NAFARELIN	HAEMORRHAGE NOS
95-02	NAFARELIN	PURPURA
95-02	NAFARELIN	STOMATITIS ULCERATIVE
95-02	NIMODIPINE	GRANULOCYTOPENIA
95-02	PRAVASTATIN	TENDON DISORDER
95-02	SIMVASTATIN	TENDON DISORDER
95-02	SUMATRIPTAN	DRUG DEPENDENCE
95-02	TERFENADINE	POLYDACTYLY
95-02	TRETINOIN	BRAIN DAMAGE CONGENITAL
95-02	TRETINOIN	CHROMOSOME DISORDER
95-02	ZOTEPINE	THROMBOCYTOPENIA
95-03	FINASTERIDE	HAEMATURIA
95-03	FLUTICASONE	ASTHMA
95-03	PAROXETINE	PRIAPISM
95-03	PRAVASTATIN	HAEMATURIA
95-03	SERTRALINE	PRIAPISM
95-06	CLOMIPRAMINE	CLEFT PALATE
95-06	CLOMIPRAMINE	MALFORMATIONS MULTIPLE
95-06	CLOMIPRAMINE	MENINGOMYELOCELE
95-06	CLOMIPRAMINE	MICROCEPHALY
95-06	CLOMIPRAMINE	PREGNANCY UNINTENDED
95-06	DANAZOL	TENDINITIS
95-06	ESTRADIOL	TENDINITIS
95-06	FELBAMATE	DEATH
95-06	FINASTERIDE	SUDDEN DEATH
95-06	FLUOXYMESTERONE	TENDINITIS
95-06	FOLLICLE-STIMULATING HORMONE, HUMAN	TENDINITIS
95-06	HEPATITIS A VACCINE	THROMBOCYTOPENIA
95-06	HEPATITIS B VACCINE	THROMBOCYTOPENIA
95-06	LEUPRORELIN	TENDINITIS
95-06	LEVONORGESTREL	TENDINITIS
95-06	MEDROXYPROGESTERONE ACETATE	TENDINITIS
95-06	MEGESTROL	TENDINITIS
95-06	RANITIDINE	CRYING ABNORMAL

Course: Adverse Reactions and Adverse Reaction Monitoring, 8-19 May 1995

Course organizer: WHO Collaborating Centre for International Drug Monitoring

Applicants and participants

COUNTRY	TOTAL	
	number of applicants	number of participants
Algeria	1	
Arab Emirates	1	
Argentina	2	
Azerbaijan	1	
Bangladesh	1	1
Belgium	1	1
Brazil	4	1
Canada	1	1
Chile	3	1
China	1	
Colombia	1	
Croatia	1	
Estonia	2	1
Georgia	2	
Germany	1	
Greece	1	1
Guatemala	1	
India	5	2
Iran	1	1
Italy	1	1
Laos	1	1
Lithuania	1	1
Malawi	2	1
Malaysia	1	1
Namibia	1	1

COUNTRY	TOTAL	
	number of applicants	number of participants
Nepal	1	1
Nigeria	1	
Oman	1	1
Pakistan	1	
Peru	2	
Poland	4	
Russia	1	1
Spain	2	
Sri Lanka	1	
Sweden	1	1
Syria	1	
Tanzania	1	1
Thailand	2	1
U.S.A.	1	1
Ukraine	1	
Uruguay	1	1
Vietnam	1	1
Yemen	1	
Zambia	1	
Zimbabwe	1	
Total	64	25

Publications from the WHO Collaborating Centre 1994/1995

1. Edwards I.R. **The WHO Drug Monitoring Programme: Current Activities.** Z. Bankowski, J.F. Dunne (eds) *Drug Surveillance: International Cooperation - Past, Present and Future* CIOMS, Geneva, 1994: 22-27.
2. Fraunfelder F.T., Edwards I.R. **Possible Ocular Adverse Effects Associated With Leuprolide Injections.** *JAMA* 1994; 10: 773-774.
3. Edwards I.R. **Future Strategies for Research in Pharmacovigilance.** *European Medicines Research: Perspectives in Pharmacotoxicology and Pharmacovigilance* 1994: 261-266.
4. Meyboom R.H.B., Fucik H., Edwards I.R. **Thrombocytopenia reported in association with hepatitis B and A vaccines.** *The Lancet* 1995; 345: 1638.
5. Lindquist M., Pettersson M., Edwards I.R., Sanderson J., Taylor N., Fletcher P., Schou J., Fraunfelder F.T. **Omeprazole and Visual Disorder: Seeing Alternatives.** *Pharmacoepidemiology and Drug Safety* (in press).
6. Fucik H., Edwards I.R. **Impact and Credibility of the WHO Adverse Reaction Signals.** *Drug Information Journal* (in press).
7. Edwards I.R. **Reply to letter to the Editor "Safety of Complementary medicines should be monitored"** *Br Med J* 1995;311:633. *British Medical Journal* (In press).

National Centres' Meeting

Objectives

1. To provide technical guidance for National Centres.
2. To formulate common technical requirements and set performance standards for the WHO Programme.
3. To identify and discuss the demand for service from the WHO Collaborating Centre.
4. To provide a forum for the debate of current drug safety issues.
5. To arrive at an advisory view on issues of importance.
6. To develop work schedules to resolve current drug safety issues.
7. To provide for the exchange of ideas and information between National Centres on methodological aspects of the Programme.
8. To provide for the development of networks for information exchange to support and encourage individuals in the field.

Terms of reference

1. Annual Meetings are primarily for the technical development of the Programme.
2. When there are related policy issues on which WHO must take a decision, the Annual Meeting may express a view, but the mechanism for formally representing the view of Programme Member Countries on the technical aspects of policy matters is through an ad hoc expert committee.
3. Polls may be taken at any stage during an Annual Meeting, but such a poll records only the feeling, balance of views or conclusion of that meeting and has no formal or binding effect beyond it.
4. A person of appropriate distinction, seniority or status within the Programme will be appointed President of the meeting and will carry responsibility for the professional integrity of the proceedings.
5. All plenary and other sessions will have a chairperson who will be responsible for the efficient management of the session itself - ensuring timescales are agreed and adhered to, objectives are achieved, disagreements are handled positively, outcomes are recorded and circulated, and so on.
6. Working groups will be staffed by a chairperson and a resource person from the Collaborating Centre. This latter person will provide knowledge and technical expertise in support of the meeting's objectives. This person will be responsible for taking and circulating notes of the session. It will be the responsibility of the chairperson to report the conclusions and recommendations of the working group back to the main meeting.
7. Working groups may report back verbally or in writing to the whole Group in which case secretarial and other support services will be provided as necessary.
8. Working groups/special interest groups will be formed from those choosing to participate in them.
9. No part of the structure or organisation of the meeting prejudices the freedom of participants from forming their own informal interest or working groups.

A request for the WHO Collaborating Centre from the participants of the
18th National Centres Meeting.

Given:

1. Unique requirements of pharmacovigilance
 - focus on drug safety
 - signal generation
 - data retrieval
2. Unique nature of the WHO program
 - the database is international
 - many countries already using WHOART alone
 - variability of resources (both financial and technical) in member countries adopting a new terminology dictionary
 - built-in expertise of WHO Centre and member countries
3. Richness but complexity of MEDDRA at this stage
 - large vocabulary, potentially cumbersome
 - uncertain maintenance and costs of distribution
 - inclusion of WHOART terms

It is suggested:

1. A subset of pharmacovigilance-specific terms most useful to coding ADR case reports be flagged within MEDDRA, and this subset begin with flagging the already included WHOART (minus the synonyms) terms.
2. This "subset" should facilitate member countries in continuing to perform their work of contributing to the WHO database, and allow them to continue to work with a system that is already familiar and technically implemented.
3. These flagged terms would be available within MEDDRA for any user to access and work with, but member countries would be encouraged to code their case reports with this subset. The subset would be made available the same way WHOART is made available today.
4. The WHO Collaborating Centre receives all case reports regardless of coding terms. Reports with subset terms will be accepted immediately. Case reports with other terms will be held for review by the collaborating centre supported by an advisory group of the programme. This group will ensure that the WHO terminology will remain sensitive both to the needs of the programme and compatible with MEDDRA
5. The WHO terminology will continue to contain only terms that are considered adverse drug reactions. Case reports with other terms will be stored separately and reviewed.

Request from participants of the meeting therefore:

The WHO Collaborating Centre should be asked to approach the ICH Expert Working Group on medical terminology with the above suggestions. It is further suggested that the collaborating centre would be responsible for creating, flagging and updating the subset of terms specifically to facilitate the drug safety / pharmacovigilance work of the programme's member countries. It should be assisted by a working group with relevant competence.

WORKING GROUP ON COMMUNICATIONS

Conclusions and recommendations

1. Communications between National Centres and WHO
 - The present lines of communications are satisfactory
 - Should be expanded to include early signals and "suspected ADR:s"
 - Include national bulletins, newsletters and publications (translated)
 - Reports should be sent with greater frequency and regularity
2. Communications between National Centres
 - Should be stimulated by regular update of addresses (fax, telephones, E-mail)
 - Conferences/exchange using DISNET, INTERNET etc. with participation of WHO Collaborating Centre
3. Communications between WHO and supranational regional centres
 - As common regulatory policies are formulated, WHO should establish appropriate channels of communication
 - The emergence of common markets (EU, ASEAN, Mercosur, NAFTA)
4. Communications between reviewers (consultants) and WHO
 - Should be improved and established on a more regular basis
 - A list of reviewers (consultants) should be circulated to all National Centres
5. The WHO data bank
 - Its use should be accessible to all enquirers, provided that
 - the CAVEAT document be followed
 - it is to the public health interest
 - relevant countries be informed that a search has been requested
 - Access is available within two weeks, but should be more timely for emergencies

Working Group on Output documents

The group briefly considered the historical background which led to the production of the correct output documents in their present form. It is recognized that the Collaborating Centre mentions a responsibility to report to national centres and that signalling needs to be frequent and regular, however in the present environment the collaborating centre's responsibility needs to be considered in the context of the volume of data submitted to national centres.

Because the group considering the documents was small it may not be entirely representative, however the limited number of participants may also be an indication of the limited application of the data by NC's at present.

The group reviewed the yearly and quarterly output documents individually and found them to have limited usefulness, in some cases because the volume of data is too great, for example New to the System, in others because the data presented are indifferent to facilitate evolution e.g. Deaths. It was agreed by the group that ALL documents are potentially of value if sufficient reviewers are available to assess them. But since we all inhabit the real world of drug monitoring with ever decreasing resources, the overall view is that a receipt of an ADR report at a NC or identification of a local problem are the prompts to initiate review of the database and prospective data reviews are neither feasible or practised.

The group suggest the signal document and ADR newsletter should be maintained and ask the centre to consider the possibility of indexing these documents.

In addition the following was proposed:

- a) Circulation of a questionnaire
- b) Inclusion of output documents in the collaborating centres training course since they often require training

And for those who don't have the opportunity to attend such a course inclusion of some explanatory data for circulation with output documents is recommended. In order to promote the recognition and development of signals it was considered that additional reviewers should be recruited.

The collaborating centre is capable of producing searches specific to the needs of National centres. The group's discussions indicated that this may not be widely known and that this issue should be emphasized together with an outline providing examples of possible search requests in the search manuals available.

**Eighteenth Annual Meeting of the National Centres Participating in the
WHO International Drug Monitoring Program
Minutes of the Working Group on Causality Determination
December 4, 1995**

Nearly 30 persons participated in the working group including representatives from Canada, France, Germany, Japan, Korea, Morocco, the Netherlands, the Philippines, Singapore, Sweden and Thailand. The working group was chaired by Dr. Ron Meyboom. Mrs. Helena Fucik was the resource person from the WHO Collaborating Centre. Dr. Philippe Duclos served as rapporteur.

The purpose of the working group was not to make decision or to reach consensus but to exchange views and information around two major questions:

1. What is the need for and purpose of causality assessment?
2. How to assess causality?

The working group started its discussions with a reminder of the difference between an adverse event and an adverse reaction which latter term assumes a certain level of causality whereas the first one only refers to a coincidental event that may be caused or not by a drug.

It was emphasized that there are three questions about causality

1. Can the drug cause the reaction?
2. Will the drug cause a reaction?
3. Has the drug caused the reaction?

These questions are of legal (regulation, compensation), scientific and medical (patient care) nature.

Some causality considerations were reviewed:

- Association (time, place)
- Pharmacology (drug action, previous knowledge)
- Medical characteristics
- Exclusion of other causes
- Quality and completeness of information

It was emphasized by participants that individual causality assessment is only one aspect of overall causality assessment. Overall assessment of a relation between a drug and an adverse events will use review of sets of reports as well as other epidemiological methods and laboratory investigations.

Causality is only part of the assessments for a given report or given drug.

Need and purpose of causality assessment?

This question must be answered first by each country that has to design its proper scheme to assess causality.

The various potential objectives include the following:

- Signal generation
- Regulatory
- Scientific
- Legal
- Public reassurance
- Education
- Push authorities to take action
- Make authorities realize some issues with thinking about it

It was generally agreed by participants that due to the workload and resources needed, it would be difficult to assess causality in all reports (cost-effectiveness). More likely there would only be a need to review selected reports depending on the objectives likely including the most serious or the ones for which causality between a medical condition and drug intake has never been demonstrated but is suspected.

Causality assessment is a tool and not a goal of pharmacovigilance.

How to assess causality?

It was proposed that in order to assess causality the following six elements of information were needed and that completeness of records was paramount to allow for causality assessment of individual report: age and sex, identified drug/adverse event, dose and route, dates/interval, course and outcome, and indications. A major caveat for causality assessment is the lack of information.

Some participants indicated that even complete information on the above mentioned variables was insufficient in many cases to allow for proper causality assessment and that the best would be to access complete medical file. Even though, at times it may be impossible to assess causality.

All countries participating in the workshop expressed strong interest with the assessment of causality but indicated various level of implementation of causality assessment.

The process by which countries assess causality is highly variable. Some countries use a very structured decentralized assessment at the reporting level which implies proper training of staff. Some others rely on special expert committees to review cases. It was generally felt that causality assessment could not be left to the reporting health care provider because of biases and the fact that, usually, reporting by a health care providers implies he/she assumes causality. For causality assessment, expertise is needed in clinical medicine, pharmacology and epidemiology.

Although one country representative suggested a simplification of the causality categories ("possibly related, probably not related, unclassifiable") most countries are making efforts to use the 6 WHO recommended categories for causality assessment and find these categories useful, although countries do not necessarily use the WHO definitions to assess causality. Actually many countries use somewhat different criteria. It was felt in particular that the definitions may not be

appropriate for vaccines.

Harmonization of the definitions and categories was perceived as highly desirable.

It was generally felt that industry should not be part of the decision making process in causality assessment but that results should be discussed with industry.

Countries expressed different policies about public access to information pertaining to causality assessment. The majority of countries however had indicated free access to this information.

Training and expertise are key to influence the quality of assessment.

General recommendations

The course on adverse reactions and adverse reactions monitoring organized by the WHO Collaborating Centre should cover in detail the issue of causality assessment

It was requested that the WHO Collaborating Centre collects information on causality assessment methods used by the various member countries so that when countries review the database they really know how to interpret causality assessment.

DRUGS OF CURRENT INTEREST LIST

Country	Drug Problem
Australia	1) Antibiotics - hepatic dysfunction (wishes to present) 2) Loratadine - cardiovascular reactions ("-") 3) Terbinafine - white blood cell disorders 4) Terbinafine - serious skin reactions 5) Dinoprostone - fetal distress 6) Dinoprostone - uterine rupture 7) Erythromycin I.V. - cardiac arrhythmias 8) Metformin - lactic acidosis 9) Coumarin - hepatotoxicity
Belgium	10) Oral contraceptives - risk of thrombo-embolic events 11) Herbal medicines 12) Vaccines
Canada	13) Terbinafine - hepatobiliary reactions (wishes to present) 14) Terbinafine - ADRs during physical activities ("-") 15) Clarithromycin - interactions, changed blood glucose levels
Canada - vaccines	16) Influenza vaccines - conjunctivitis
France	17) Sparfloxacin - photosensitivity (wishes to presents) 18) Pharmacovigilance of the blood derivation products ("-") 19) Fibrates - muscular adverse effects ("-") 20) Terbinafine - ADRs ("-") 21) Pharmacovigilance systems outside the European Union 22) Pharmacovigilance system for vaccine products
Hungary	23) Clavulanic acid - skin reactions (wishes to present) 24) Gestodene & desogestrel OCs - thrombo-embolic events 25) Felbamate - ADRs
New Zealand	26) Omeprazole - arthralgia (wishes to present) 27) Omeprazole - polymyositis ("-") 28) Sumatriptan - chest pain ("-") 29) Sumatriptan - autonomic imbalance ("-") 30) Sumatriptan - bradypnoea/ apnoea ("-") 31) Bezafibrate - angina ("-") 32) Patterns of reporting in the IMMP ("-")
Singapore	33) Vaccines - various ADRs
Sri Lanka	34) Policies and criteria for registration of new drug substances 35) Gestodene preparations - thrombo-embolic events
Thailand	36) PRS of Artesunate and Artemether

VACCINE-ASSOCIATED ADVERSE EVENTS REPORTING: ISSUES AND PRIORITIES



Specific issues related to vaccines (1 of 2)

- Vaccine usually given to healthy individuals
- Low tolerance for adverse events
- Variation in need and perception with variation in disease control
- Due to the large number of vaccinations, many coincidental adverse events
- Causality assessment difficult
- Need for special expertise in causal assessment



Specific Issues related to vaccines (2 of 2)

- Much less products (30 versus 20,000)
- Problem of "cocktail" vaccines
- Lot-by-lot surveillance
- Need for vaccine distribution data



Important aspects

- Could the vaccine cause the event?
- Did the vaccine cause the event?
- Dissemination of results

- Importance:
 - Causality assessment
 - Communication



Importance of programmatic errors



Current situation

- In many cases, surveillance linked with disease surveillance programs
- Tremendous variation in reporting process according to countries
- At times lack of communication between immunization programs and drug monitoring programs



Main discussion elements

- Difference in reporting procedures
- Appropriateness of current program for vaccines
- Causality assessment
- Recommendations to improve reporting



Proposals (1 of 2)

1. Regular session to discuss vaccine-associated adverse events reporting during the meeting of the national centers
2. Need to have list of people specifically interested with vaccine monitoring
3. Need for better communication with vaccine programs and to invite people dealing with vaccine-associated adverse events to participate in meeting



Proposals (2 of 2)

4. Possible participation in vaccine-adverse events discussion up on internet
5. Encourage countries to transmit information on vaccine-associated adverse events to WHO database
6. If new program in a country, most likely need to implement a system as part of immunization programs and disease surveillance
7. Need to foster exchange between drug programs and immunization programs to help improve clinical trials for vaccines
8. At a later stage, need to look at the way information on vaccines is kept in WHO database

