SPECIAL ARTICLE

Drug Saf 2010; 33 (7): e1-e23
0114-5916/10/0007-0001

WHO's International Drug Monitoring – The Formative Years, 1968–1975

Preparatory, Pilot and Early Operational Phases

Jan Venulet[1] and *Margaretha Helling-Borda*[2]

1 Senior Advisor to CIOMS, Geneva, Switzerland
2 Independent Public Health Consultant, Commugny, Switzerland

1. Background and Introduction

In early 2009, Jan Venulet (JV), gratefully agreed to the suggestion by the President of the International Society of Pharmacovigilance (ISoP) to write 'a chapter or two' on the earlier periods of pharmacovigilance. The purpose of ISoP's project, to which several others will also contribute, is 'to collect the memories of the beginning of pharmacovigilance with the objective to put it on the website for future generations'.

The second author, Margaretha Helling-Borda (MHB), invited by JV to collaborate on this walk down memory lane of the WHO's International Drug Monitoring, was also part of the early and formative years, 1968–1975.

Our starting point for refreshing our memories was JV's own library and numbered references from which we selected relevant publications from the 1960s and 1970s and unpublished WHO documents. Among the latter, one in particular has been a major reference source (seemingly the only existing copy) entitled ''Pilot Research Project for International Drug Monitoring – Assignment Report, 9 January 1968–10 March 1970 by Dr Jan Venulet, Senior Project Officer''.

Apart from the above, together with World Health Assembly (WHA) Resolutions (Appendix 1), our other primary reference sources in writing this paper have been:

- Presentation at the 25th Anniversary of the World Health Organization's Programme for International Monitoring by Jan Venulet. In: Proceedings of the XXVIIth CIOMS (Council for International Organizations of Medical Sciences) Conference in Geneva (organized jointly by CIOMS and WHO), 14–15 September 1993.
- ''Experience with the World Health Organization: International Monitoring of Adverse Reactions to Drugs'', WHO, Geneva, by Margaretha Helling. In: Tognoni and Vander Kleijn, editors. Clinical Pharmacy and Clinical Pharmacology. Gouveia. Chapter 9, 141–151, 1976.

For a further list of references and selected bibliography, see Appendix 2.

The following is a brief summary of the history, development, activities, outputs, results and reflections of the formative years, 1968–1975, of the WHO International Drug Monitoring.

2. Why and How did WHO get Involved? A Bit of History

In 1957, thalidomide was introduced in Europe. It was widely prescribed as an allegedly harmless treatment for morning sickness and nausea. In 1961 came news of the thalidomide disaster. Thousands of babies had been born with phocomelia and micromelia in many countries. More and more this bleaker side of therapeutics began attracting attention among physicians and pharmacologists. Health authorities in several countries began collecting reports on adverse drug reactions (ADRs), and various systematic

drug monitoring programmes were initiated. The WHO was requested to take an active role in assuring the safety of drugs. That is *why* the WHO got involved.

In 1962, 6 months after the thalidomide disaster became known, the WHO's WHA, which meets every year in May, recognized the seriousness of drug safety problems and recommended first measures for dealing with these problems. Afterwards, each WHA adopted a more specific resolution (summarized in table I) than the previous, culminating in 1967 in Resolution 20.51, which laid the basis for the international system of monitoring ADRs.

The 1967 resolution WHA20.51 is worth quoting here in the text, because that is *how* the WHO got the WHA mandate to start the Pilot Research Project for International Monitoring of Adverse Reactions to Drugs, with initial financial support from the Government of the USA:

''Having noted the report by the Director-General; and

Recalling resolutions WHA18.42 and WHA19.35 on the monitoring of adverse reactions to drugs,

1. NOTES with appreciation the agreement reached between the Organization and the Government of the United States of America concerning a grant for the WHO pilot research project on the modalities of an international system of monitoring adverse reactions to drugs; and

2. REQUESTS the Director-General to take the necessary measures for that pilot project to be carried out and to report on its results to the World Health Assembly.''

Table I. 1962–1967 WHA Resolutions on serious drug safety problems (see Appendix 1 for full texts)

1962 WHA15.41 Clinical and Pharmacological Evaluation of Drugs
1963 WHA16.36 Clinical and Pharmacological Evaluation of Drugs
1964 WHA17.39 Clinical and Pharmacological Evaluation of Drugs
1965 WHA18.42 Adverse Drug Reaction Monitoring System
1966 WHA19.35 International Monitoring of Adverse Reactions to Drugs
1967 WHA20.51 WHO Pilot Research Project for International Monitoring of Adverse Reactions to Drugs

Handb. Res., 8th ed., 1.3.3 Twelfth plenary meeting, 25 May 1967

(Committee on Programme and Budget, ninth report)

Under the grant referred to in WHA20.51, the US Government provided, for the duration of the pilot project of 3 years, office space and equipment, computer facilities, advice and financial support. It is of interest that this grant was the result of direct involvement and statement by the President of the United States, Lyndon B. Johnson, as seen from the letter below:

THE WHITE HOUSE

Letter from the President to the Secretary of Health, Education and Welfare, John W. Gardner (Excerpts)

Dear Mr Secretary:

I authorize you to perform the functions as may be required to provide assistance by the United States in the World Health Organization International System to Monitor and Report Adverse Reactions to Drugs.

I am pleased that the grant made possible by this delegation of authority will enable the World Health Organization to develop a worldwide early warning system for drugs, similar to the system now in development in the Food and Drug Administration. The World Health Organization's international drug reactions monitoring system will help prevent widespread tragedy of the sort which resulted from the use of thalidomide.

Sincerely, /s/ LYNDON B. JOHNSON

3. Preparatory Phase: Up to 1967 – WHO Headquarters, Geneva

As soon as it was decided to implement the project, an immense amount of preparatory work began at WHO Headquarters in Geneva, sorting out technicalities with the US FDA, planning, the recruitment of staff, and modes of collaboration and administrative support from the WHO Regional Office for the Americas (AMRO), as the project was to be located in the USA. All this preparatory work was in the hands of Dr Bruce Royall, Chief of the WHO Headquarters Drug Safety Unit, who for some years had been preparing the necessary background papers, reports

and other documentation, and Dr Hans Halbach, Director of the WHO Headquarters Division of Prophylactic and Therapeutic Substances. Without any doubt it was the quality of these preparatory steps, and the recruitment of the right people, which assured the successful development of the project.

Among the background documents prepared in Geneva before the start of the Pilot Research Project for International Drug Monitoring was a useful list of ADR terms, basis for the pilot project's further deliberation. Dr Barbro Westerholm from Sweden and Dr Bill Inman from the UK were involved in preparing this list, reviewed among other topics, at a preparatory meeting in Geneva in November 1967.

Resulting from the meetings and reports of several WHO scientific groups, it was decided that, during its pilot stage, the project *objectives* were to:

(a) assess the feasibility or otherwise of an international system of drug monitoring;
(b) develop the methodology for recording case histories of adverse reactions to drugs, systems for analysis and feedback of data to national monitoring centres;
(c) undertake analysis of in-stored data on an experimental basis;
(d) provide facilities for searches by WHO staff and national centres on the types and patterns of adverse reactions to individual drugs;
(e) make a preliminary study of the contribution of drug monitoring to research in pharmacology and therapeutics.

A 3-year period of operation had initially been considered as the necessary minimum of time required for meeting the above objectives. However, the real time period the project operated since the first staff member (JV) was recruited was, at the time, evaluated to be about 2 years, taking into account difficulties and delays in recruiting the rest of its planned staff.

4. Pilot phase: 1968–1970, Alexandria, Virginia, USA

All organizational steps prior to the inception of The Pilot Research Project for International Drug Monitoring had thus been handled by WHO Headquarters, Geneva, as described above.

4.1 Start

The WHO Pilot Research Project for International Drug Monitoring *started* its operation in Alexandria, Virginia, USA, on 7 February 1968 with the arrival of JV, after briefing at WHO Headquarters. He became Senior Project Officer, in charge of the activities of the project, an interregional project under the authority of WHO in Geneva. In WHO's organizational structure the project was given the abbreviation RDM.

The reason why the project was located in Alexandria, Virginia, was the proximity to the US FDA which then had its headquarters in Arlington, Virginia.

4.2 Administrative Help from the WHO Regional Office of the Americas (AMRO)

The AMRO in Washington was responsible for having located the project premises in Alexandria, Virginia, plus initial administrative procedures, recruitment of secretarial staff and other personnel related matters. The Library was put at the disposal of the project and agreed to circulate publications of interest. AMRO further provided a large proportion of the office supplies and transportation from Washington to Alexandria when the need arose. The WHO Regional Director and his administrative staff took a particular interest in the project.

4.3 Grant from the US for Rental of Premises, Use of FDA Computers, etc.

The FDA of the United States government, in its capacity as grantor (close to $US300 000 during the pilot phase) gave access to FDA facilities, computers and printers; without these the project's computer data processing activities would have been impossible. In addition to the grant, the FDA also made available the equipment necessary for the production of standard project documents from computer printouts. The FDA library was accessible to the project and

gave excellent service. The rental costs for the Alexandria premises were also settled by the FDA, as well as furniture and office machines, as part of the grant agreement.

4.4 'Smooth Functioning'

The role of the WHO Headquarters, the cooperation from AMRO and the FDA, and the crucial financial support from the FDA contributed greatly to the smooth functioning of RDM. Faced with a very limited time to meet the pilot project objectives, RDM professional staff were able to concentrate on methodology and scientific matters, instead of having to be bogged down with too many administrative and financial concerns. Basic administrative guidelines were developed early on (20 March 1968, ''Administrative Procedures for the WHO Pilot Research Project for International Drug Monitoring'').

4.5 Staffing

Twelve positions were assigned to the project, and WHO Headquarters recruited the professional staff, i.e. two medical officers (JV and Lloyd Christopher, and, for a short while, J. Woodward), one pharmacist (Margaretha Helling), one statistician (Alvaro Aldama), one systems analyst (Sam Molander), one programmer analyst (Esko Ahlroth), one technical officer (a nurse; Cathy Skura) and one administrative technician (Ted Webster). AMRO did the recruitment of secretarial and clerical staff. In all, ten nationalities were represented: Canada, Finland, Columbia, Mexico, the Philippines, Poland, Sweden, Trinidad and Tobago, the UK and the US. An Indian colleague, a statistician, (K. Patwari), also joined the project for a few months on a short-term assignment. It was thus a very heterogeneous group, even by WHO standards, mostly newcomers to the US, with different commands of English, different backgrounds, etc., but with a lot of competence, goodwill and enthusiasm to take up the challenge, and who, during the development of the project, also became very good friends.

4.6 Participating Countries

Ten countries, all with national drug monitoring centres, participated in the pilot phase. These were as follows:

- Australia (headed by Dr Anette Welshe)
- Canada (Dr Ed Napke)
- Czechoslovakia (Prof. O. Smahel)
- The Federal Republic of Germany (Dr G. Homann)
- the Netherlands (Dr Leo Canta)
- Ireland (Dr A. Scott)
- New Zealand (Dr G. McQueen)
- Sweden (Dr Barbro Westerholm)
- The UK (Dr W. Inman)
- The USA (Dr A. Ruskin).

The first WHO meeting of representatives from the National Centres and some outside invited experts (Prof. Lee Cluff from the US, Prof. D. Finney from the UK and Dr N. Irey from the US), took place in Alexandria, Virginia, in September 1968. The second meeting was held in Geneva in November 1969.

4.7 Main Initial Pilot Project Activities

Based on the objectives, the main initial activities of the pilot phase were directed towards the production of the following:

- A drug reaction reporting form
- An adverse reaction dictionary
- A drug dictionary
- The development of a suitable computer system for data processing
- The production of output documents
- The development of a computerized system for alerting or signalling of increase in reporting
- The development of an information retrieval system.

4.8 Adverse Drug Reaction (ADR) Reports, Reporting Forms, Guidelines, ADR and Drug Dictionary Methodology Development, etc.

The Assignment Report prepared by JV for the period 9 January 1968 to 10 March 1970 describes in details the above, plus much more. The

35 annexes of that report include, for example, samples of all output documents, content and statistics of incoming reports, forms and flow of the coding of the ADR reports, samples of the ADR terminology and the drug dictionary, time-studies undertaken, flow-charts of activities and progress, and the systems analysis and computerization of the data. As all this is much too voluminous to discuss in this article, we have summarized only the most relevant areas from the assignment report and from other documents, in particular, as already mentioned in the introduction, JV's presentation at the 25th anniversary of the WHO International Drug Monitoring, at the CIOMS Conference (organized jointly by CIOMS and WHO) in 1993 in Geneva. Papers on the overall methodology were also published in 1971–1974, covering in more detail the development and content of the ADR terminology (e.g. Royall and Venulet in 1972, Venulet 1973) and the drug dictionary (Helling and Venulet in 1974) [see Appendix 2].

4.8.1 ADR Reports and Reporting Forms

During the 2 years of the pilot phase the Centre received more than 24 000 case reports. The original reporting form that we developed required cumbersome transcribing and was soon replaced by an improved version suitable for both national centre reporting and for monitoring coding and card punching. Yes, card punching; light years away from today's technology! With some modifications, the ADR reporting form is still used today, except where it has been replaced by direct computer input.

Guidelines on how to complete the ADR reporting forms were developed, both for the project and for the national centres.

4.8.2 ADR Dictionary, Terminology and Structure

The participating centres were using the adverse reaction terms used by the reporting doctors, translated into English if necessary. At first, for computer input, the more restrictive adverse reaction terminology list prepared by Barbro Westerholm and Bill Inman before the start of the project was used; it was later extensively revised during the course of the project.

A three-tier ADR terminology was developed:
1. *'included terms',* which were synonyms with 'preferred terms';
2. *'preferred terms',* which were the terms recorded on the drug reaction report for computerization;
3. *'high-level terms',* which grouped closely related preferred terms under the same term.

Terms describing adverse reactions affecting different body systems, e.g. cardiovascular, renal, central nervous system or skin, or certain types of suspected ADR, such as resistance mechanism disorders or application-site disorders, were grouped into system organ classes, with the provision that a term could be part of up to three system organ classes (30 in total). This added flexibility for output and retrieval.

An example of the three-tier terminology is: nerve pain (included); neuralgia (preferred); neuropathy (high-level); in the system organ class 'Central and peripheral nervous system disorders'.

In the development of the ADR terminology, the contribution of Lloyd Christopher was notable. The WHO Adverse Reactions Terminology included only reported suspected ADRs, which were added to the Terminology as they were reported. Its structure and contents has remained, to a large extent, unchanged. Time has proved it a useful tool but it naturally undergoes periodic revisions at the Uppsala Monitoring Center (UMC), which took over the activities of the International Drug Monitoring Centre when it moved from WHO Geneva to Sweden in 1978.

4.8.3 Drug Dictionary: Purpose, Scope and Structure

A complex problem to handle was that of drug names. The project had to develop a system for thousands of names of active substances marketed under even more trade names, as single-active-ingredient drugs or as combinations of ingredients. The second author of this paper, MHB, was responsible for designing the system to permit a more sophisticated analysis of data. Two classifications of drugs were also developed – a pharmacological one for mechanism or site of action, and a therapeutic one for clinical application. After wide consultation, JV

produced these, which, after the transfer of the Centre to Sweden, were replaced by the now more universally used Anatomical Therapeutic Chemical (ATC) classification, developed in Norway.

The purpose of the Drug Dictionary, developed during the pilot phase, was to enable grouping of reported drugs containing the same active ingredient(s) and/or belonging to the same pharmacologic classification and/or the same therapeutic classification. The drug dictionary was (and still is) an open-ended document and did not include all drugs in all ten participating countries. Although continuously updated and expanded, it was limited to those drugs reported to the project as 'suspected' or 'other'.

It may be of interest here to expand a bit on the initial design and development of the Drug Dictionary (described in detail in the 1974 publication by Helling and Venulet) as it eventually became a major source of income for the UMC, with, of course, modifications and updates suited for modern technology and needs. The basic concepts, however, seem to have remained. These were to maintain the original drug name reported on the ADR report submitted to the project, whether this was a trade name, nonproprietary name, chemical name or code number.

After verification of the drug standard spelling, according to the official drug lists (these were few in 1968 and no standard computerized national files existed at the time) or the selected one of the participating country, the reported drug names, mostly trade names, were entered on a separate 'DC-2' coding sheet designed by the project. Also entered on the coding sheet was information on whether the drug was a single (S) or multiple ingredient drug (M), the number and names of active ingredients under the chosen nonproprietary name, the reference source of the drug name, a manufacturer's three-letter code, and the alpha-numeric pharmacologic and therapeutic classifications. Single ingredient drugs were linked through the RDM preferred name, which was the WHO International Nonproprietary Name (INN) when it existed, otherwise the International Pharmacopeia Name (IPH) or, when these did not exist, a nationally approved or other name was chosen.

A separate part of the Drug Dictionary was the Multiple Ingredient File. Here the drugs were organized in order of number of active ingredients included in each mixture. Each multiple ingredient and its active ingredients were assigned a unique record number. When entered into the drug dictionary, a computer programme was designed to link those drugs that had the same active ingredient(s). The combination first reported to the project was selected as the preferred name. Combination drugs were much more frequent back in the 1960s when safety assessment for drug registration and evaluation was in its infancy.

The Drug Reference List, a cross index with all reported drug names and accompanying information, became a major and regular output of the Drug Dictionary.

As the Drug Dictionary was being developed, cooperation with others took place, in particular with the FDA, the American Medical Association and the Pharmaceutical Unit (PHARM) at WHO Headquarters where Agathe Wehrli was responsible for the INN work. To assist in computerization of the INN data, manually handled at the time, the pilot project designed a record layout for keypunching and took care of keypunching of 2400 Xerox cards with INN information (Latin, English and French names, the INN request number, the proposed INN list number, the recommended INN list number, the code for any objection filed against the name and accepted names differing from the INN). A magnetic tape and a sorting programme for printouts of INN information resulted and greatly facilitated the PHARM work. The Drug Dictionary also became an important tool towards creating the first computerized Swedish drug regulatory data base. Rolf Sjöblom from the Swedish Drug Regulatory Authority collaborated with the programme on this. Later on into the 1970s, Per Manell at the same institution developed this work further.

4.8.4 Development of a Suitable Computer System for Data Processing and Retrieval

Practical operations of the project – input of case reports, quality checking of different items of data, and the development and maintenance of

different files and retrieval formats – would not have been possible without the immense contribution of the project's systems analyst, Sam Molander, assisted by Esko Ahlroth. In those days these were difficult tasks, practically without software packages; every operation had to be analysed, designed and programmed from scratch. It took some time for those in the project less acquainted with data processing to acquire the minimum essential knowledge in this domain, indispensable for mutual understanding. Ted Webster had the difficult task of seeing that the administrative procedures were strictly followed.

In order to produce documents of acceptable quality for distribution, and with minimum errors, many time-consuming programmes were prepared, including programmes for statistical analysis of the stored data and provisions for future additions of new participating countries. In under 2 years, approximately 110 programmes were designed; however, it was already predicted that if the pilot phase would proceed into a primary operational phase, an extensive revision of the computer system would be needed for efficient and economic handling of updating procedures, information retrieval and summary reports.

Some historical computer data may be of interest here. The computer provided by the FDA through the Consumer Protection and Environmental Health Service in Washington had the following configuration: one processing unit IBM System/360 Model 50; two 2314 direct Access Storage Facilities; three 2311 Disc Storage Drives; seven 2401 Magnetic Tape Units; two 1403 Printers; one 2540 Card Read/Punch; and one 2501 Card Reader. The computer system operated under the IBM 360 Operating System allowing multiprogramming with a fixed number of tasks. For the programme development, the language PL/1 was used and, when applicable, the IBM standard sort and utility programmes. A master file, an adverse reaction dictionary and a drug dictionary were thus produced, plus a system for different external and internal summary reports; a system for producing signals on a significant increase in drug reaction reporting; and a system for providing searches in the master file containing the drug reaction reports.

4.8.5 The Production and General Concept of Output Documents

Generally the output from the project fell into five main categories:

- reference reports
- scanning reports
- signal reports
- retrieval reports
- supporting documents

(For a detailed list of output documents see table II.)

The proper use of data as numerous and varied as those processed in the project required a retrieval system and outputs capable of satisfying predetermined needs. But these had to be flexible enough to enable staff to retrieve other information, as indicated by changing interests, and to follow up various leads and suspicions generated by the scientific approach. Apart from the already mentioned Drug Reference List and the

Table II. Detailed reports and other documents regularly produced by the WHO Centre from 1971

Report type	Main data contents
A (reference)	Drug names, followed by associated adverse reactions
B (reference)	Adverse drug reactions, followed by associated drug names
H (signalling)	Survey on increase in reporting on a drug or a drug/adverse reaction combination
K (signalling)	Drug/adverse reaction combinations new to the system (first time reported)
L (signalling)	Drug/adverse reaction combinations of possible interest: selected in cooperation with national centres
M (signalling)	Most reported drugs (responsible for 30% of total input)
N (signalling)	Reports with 'death' as outcome or as suspected adverse reaction
P (signalling)	Reports with fetal disorders
D (signalling)	Reports with drug dependence
Drug reference list	List of all reported active substances, INNs and trade names cross-referenced and with additional information
ADR terminology	Structured list of adverse reaction terms used for computer input and retrieval
Drug comment	Prepared by Centre's staff; the first step in evaluation of a drug safety problem
Search request	A document containing retrieved information based on specific parameters

Adverse Reaction Terminology, two types of reference reports were developed. They contained basic information on all drugs and all adverse reactions reported to the system. Report Type A had drug name as the main entry, followed by a list of suspected ADRs associated with each drug. Report Type B contained the same information, but the main entries were the adverse reaction terms. Today, document Type A is still produced.

One purpose of the project was to aggregate single case reports of rare and unusual reactions from different countries, which otherwise would not attract attention.

4.8.6 Signalling System and Reports

Considerable effort was devoted to the identification of changes in the flow of data and types of individual case reports that might indicate a drug safety problem, and to translate this into computer programmes so that the occurrence of any such event would be signalled automatically.

This led to the development of a signalling system of quantitative and qualitative signalling reports.

The first signal was 'Increase in reporting' (quantitative) on a drug in general or on an association between a drug and an adverse reaction. It was based on statistical testing proposed by our statistician, Alvaro Aldama, and developed further by Guillermo Belleno and K. Patwary. The system provided information on (i) drugs, adverse reactions, and a combination of both, reported for the first time to the project; and (ii) increase in reporting of drugs, adverse reactions and combinations of both above a certain level. The ratios chosen for comparisons were:

$$\frac{\text{Reports to drug X in this batch}}{\text{Total reports in this batch}}$$

$$\frac{\text{Reports on Drug X in Master File}}{\text{Total reports in Master File}}$$

From the start, an increase in reporting above an 80% probability level was operative.

In Appendix 3 the original communication (Information sheet no.17 of 31 January 1975), with details of the development and evolution of the "Increase in reporting" signal, Report type H, are shown, together with the statistical formulae used.

Another signal listed 'Most reported drugs' (qualitative) – namely, drugs responsible for 30% and more of the reports. It was presented as Report type M.

Still another signal, designed to draw attention to single case reports of serious or new and unexpected ADRs, was called 'New to the system' (qualitative), or Report type K. The computer was programmed to retrieve and print from every new batch all ADR combinations not already known to the system. These were communicated to all national centres with the request to check combinations of interest to them. These, in turn, were reintroduced into the computer in such a way that whenever reported again a signal (qualitative) would be generated up to a certain total or during the following 12 months.

The last group of signals represented case reports with certain types of ADR, such as death, malformation, drug dependence: Report types N, P and D, respectively.

Some of the above-mentioned signals are still operational and in use.

Ad hoc needs for information, in particular of participating national centres, could be satisfied by means of 'special search' procedures specially developed for that purpose.

All output documents were circulated to participating national centres and evaluated by the centre's staff.

4.9 Successful Outcome of the Pilot Project Phase: Decision to Enter Primary Operational Phase

During both the WHO Meeting of Investigators on International Drug Monitoring, September 1969, and the WHO Meeting of Consultants on International Drug Monitoring, November 1969, the progress of the project was analysed, and conclusions and recommendations included in respective reports. In general, they considered that the project had met its objectives and accumulated enough evidence, indicating the feasibility of an international system of drug monitoring. They also recommended the next

primary operational phase in the nearest future, even though the project had only operated for less than 2 years at the time of these 1969 WHO meetings.

In May 1970, the outcome of the pilot phase was positively evaluated by the WHA. Resolution WHA23.1 requested the Director-General to develop the activities of the project into a primary operational phase aimed at establishing an international system for monitoring adverse reactions for alerting Member States in case of urgency.

Excerpts from resolution WHA23.13, May 1970:

"*4. REQUESTS the Director-General to explore the possibility of financing the project from sources other than the regular budget bearing in mind the views expressed in the discussions at the Twenty-third World Health Assembly.*

5. DECIDES that subject to (4) above:
(a) the project shall be financed for 1971 firstly by postponing the addition of $100.000 to the revolving Fund for Teaching and Laboratory Equipment and secondly by withdrawing the balance from the working Capital fund: and that the Director-General be requested to reimburse the working Capital fund up to 245.000 from any operational savings that could be effected under the regular budget for 1971;
(b) provision be made for 1972 and subsequent years for the necessary financing of the project by means of the regular budget.

6. DECIDES that as soon as the necessary arrangements can be made, the project shall be based at WHO Headquarters in Geneva."

(See Appendix 1 for full text of this and other resolutions mentioned in this paper.)

5. Early Operational Phases: 1971–1975, WHO Headquarters, Geneva

The immediate consequence of the decision taken at the 1970 WHA was the transfer of the project to WHO Geneva to embark on the primary operational phase. This took place towards the end of 1970. The name "WHO Research Centre for International Monitoring for Adverse Reactions to Drugs" was now generally being used; within WHO, it was still referred to as RDM.

The main reasons for the decision to move to Geneva were the central location, in the premises of the WHO Headquarters, and access to the WHO computer facilities. But more independence, resulting from not being located in one of the participating centres, played a part also.

5.1 More Countries Joining, More Global Contacts and More Analysis of Data

With the satisfactory completion of the pilot phase, more countries became members. In January 1971, national centres in Denmark and Norway joined the WHO International Drug Monitoring activities; in April 1972, centres in Israel, Japan and Poland joined; in 1973 Yugoslavia, Finland and France joined; and in 1974, Romania and Bulgaria also joined, bringing the total number of participating countries to 20.

With more emphasis placed on alerting in case of urgency, the Centre's staff became more involved with the analysis of the accumulated data. An important regular addition to the output documents were 'Drug comments' (see two original examples in Appendix 4) based on clues derived from our signalling system, compared with the data from the literature and commented upon. Here, the contribution of Dr Edmund de Maar was of particular importance. Others contributing to development in the early operational phases were the pharmacist Peter Heslop, and the biostatistician Steve Mandel who collaborated with David Finney on 'Signaling of Adverse Reaction to Drugs' and published on the subject.

The Centre also undertook pioneer methodological studies to analyse the cost of ADRs. These were done by Dr E. Mach and JV, and published in the WHO Chronicle 1975 (see Appendix 2: references and selected bibliography). Moreover, drawing from the epidemiological work with the collected data, JV coined the term 'pharmacoepidemiology' or 'epidemiological pharmacology' and first described the methods of work under this specialty in the International Journal of Clinical Pharmacology in 1974, and subsequently in other publications in 1978 and

1999 (see Appendix 2: references and selected bibliography).

The Centre did not publish or report on associations between drugs and adverse reactions; this was not its responsibility. It did, however, publish papers on methodology of drug monitoring, epidemiology of drug use, economics of ADRs as mentioned above, and related topics, as it felt an obligation to share its experience. Up to 1975, a number of papers were published (see Appendix 2: references and selected bibliography).

The Centre had the privilege to work with and get advice and input from a great number of prominent international experts in specific scientific fields related to ADRs. It received many visitors, and the staff was regularly in contact with and visited scientific and medical institutions, national centres and regulatory bodies in the participating countries, and took part in international conference and meetings.

6. Results

There is of course the big question of what was all of this good for? What were the results? To answer these questions, several aspects of the activity need to be considered: general and specific, immediate and delayed.

A particularly valuable, although unforeseen, effect has been the creation of a network of people in regulatory agencies who know one another well and are ready to discuss matters and advise one another. The industry at first deeply mistrusted the programme. Certainly the data were weak, and fears that unjustified alarms would do more harm than good were widespread. However, the system stood the test and the Centre was never blamed for an unjustified action. In addition, the respect was mutual. In those days, JV was advised to avoid any contact with industry. But slowly many joint projects, as well as other forms of cooperation, started, and have developed over the years for the benefit of public health.

The Centre did not lag behind the professional media in recognizing drug safety problems, except of course when case reports were sent elsewhere. The Centre did identify through its signalling system several associations between drugs and adverse reactions, and brought them to the attention of national centres (see table III), which at times recognized the validity of the signal and took necessary steps.

In the 1993 CIOMS Conference in Geneva (organized jointly by CIOMS and WHO) commemorating the 25th Anniversary of the World Health Organization's Programme for International Drug Monitoring, JV said the following to which he still adheres: "Single case reports are frequently criticized as not being substantial enough to reveal a new drug safety problem. I disagree. The potential of single case reporting was best demonstrated some years ago by Venning (see Appendix 2). In a long list of recently discovered adverse drug reactions, the first signal was a single case report in a medical journal. This confirms the value of single case reports and of alert observers. Publication in a medical journal is likely to attract more attention among doctors than the submission of a report to a manufacturer or drug regulator. I suppose that not enough attention is given to the differences in 'alerting power' of a case report according to where it is submitted."

7. Some Final Remarks and Reflections

From JV:

First I want to quote, again, what I said at the CIOMS Conference in 1993. It is still valid.

"The programme was to me a particular challenge. As a physician specialized in experimental pharmacology, I had worked for many years with the rigor of experimental sciences, characterized by clear hypotheses, standardized conditions, statistical evaluation of results, etc. In other words, trying to approach the ideal situation of studying the effects of a single variable. And then, in this project, I was exposed to the other extreme, of a retrospective analysis of frequently incomplete and poorly documented case reports of suspicions, sent in by health professionals from different countries, cases of patients frequently taking many drugs, etc. In short, an unknown number of unknown variables. Hoping to find among this mass of reports cases of medical significance amounted to what Bill Inman compared to looking for nuggets of

Table III. Examples of recognized drug safety problems (up to 1974)

Drug/adverse reaction	Date of signal recognition by the WHO Centre	Follow-up by national centre	Action
1. Clindamycin/colitis	30.03.1973	16.08.1974	Dear Doctor letter (USA) Regulatory warning in 1976 (UK)
2. Erythromycin estolate/jaundice (see appendix 4 for details)	30.03.1973	28.11.1973	Warnings by CSM (UK) and ADRAC (AUS), withdrawal in Sweden
3. Penicillamine/nephropathy	30.09.1972	1974	Warning publication in Deutches Aerzteblatt 1974; 71: 197
4. Tilidine/dependence (see appendix 4 for details)	31.12.1972	1974	Publication in The Pharmacologist, 1974; 16; 247. Registration refused in Finland
5. Heparin/syncope, dizziness	30.09.1972	20.01.1973	Manufacturer returns to formerly used preservative
6. Oral contraception/pregnancy unintended	30.09.1972 (interaction through enzyme induction)	01.06.1974	Article in The Lancet 1974; II; 1113 (similar findings reported)

ADRAC = Adverse Drug Reactions Advisory Committee which is a subcommittee of the Australian Drug Evaluation Committee; **CSM** = Committee on Safety of Medicine in the UK.

gold in a huge pile of garbage. It took me some time to convince myself that it was possible. Our objective was to devise methods to find these nuggets of gold, if there were any! Though, fortunately, there were no tragedies of the dimension of that caused by thalidomide, the Centre made some valuable contributions, in some cases in raising valid suspicions and, in others, in providing additional data supporting the original observation and amplifying awareness of a particular drug safety problem.

All of this was possible thanks to the competence and enthusiasm of all of my colleagues, first at Alexandria, Virginia, and later here in Geneva, the advice of numerous consultants over the years, and the help and understanding of participating national centres. Let me thank all of them on this particular occasion again.''

To expand on the above, I would like to add something I feel strongly about; the reasons why so much work could be done during the short time of the pilot phase. The group that had been recruited during the pilot phase could be likened to a full-time task force 'in which people of different disciplines, scientifically and administratively, could devote full-time to their own specialty but, within a team, work to meet the set objective of the task force'. We had an enviable professional independence, without usual bureaucratic interferences of a big organization. We were judged on the results.

From MHB:

For me the formative years of the project were also the formative years for me, professionally and personally. I had the great opportunity to work in an international setting, in a diversified team that contributed to a worthwhile cause – avoiding another thalidomide disaster. At times I had to be reminded that methodology development was the aim of the project and not the jumping to quick conclusions on causal relationships between a drug and its adverse reactions.

It was exciting and a privilege to be part of a 'first' and to be under a certain time pressure to deliver. I benefitted greatly from the learning experiences in the project in other WHO 'firsts', such as in the WHO essential medicines programme. I am more than ever amazed how a comparatively small sum of money, the US government grant of around $US300 000, gave the impetus to start the WHO International Drug Monitoring; how it could be 'stretched' that far to make it possible to meet the project objectives in such a short time; and to be the catalyst for embarking on a long and successful journey.

8. What Happened Next?

It may be of interest to add here what happened to the WHO Centre for International Drug Monitoring between 1975 and 1978 when it moved to Sweden.

JV left WHO in 1975 because of the withdrawal of agreement by the Polish government of those days. He went on to become visiting Professor in Clinical Pharmacology at the Geneva University. Later he became head of intensive surveillance at Ciba-Geigy, spending a lot of work in such areas as establishing, in a more objective way, the causal relationship between the drug and the suspected ADR. He is still active and has been, for several years, senior advisor to the Council for International Organizations of Medical Sciences.

MHB acted for a while as Project Leader for the WHO Centre for International Drug Monitoring until Dr J.F. Dunne joined WHO as responsible person for the Centre. In 1975, the WHO and the global scene changed when developing countries requested assistance from WHO. In the report to the 28th WHA, the WHO Director-General reviewed the main drug problems facing the developing countries and outlined possible new policies. In 1975, resolution WHA28.66 became the basis and mandate for the WHO essential medicines list and programme in which MHB became involved from the start, and later became a Director for the Action Programme on Essential Drugs (DAP). Since retirement from the WHO, she has been an independent public health consultant and is still active.

With insufficient funds to run both a new programme (essential medicines) for developing countries and the Centre for International Drug Monitoring for Adverse Drug Reactions, WHO was very grateful to the Swedish Government when it offered to finance the latter and establish a WHO Collaborating Centre in Uppsala, Sweden. The move took place in 1978. This was preceded by negotiations during 1975–1978, between the WHO's Director-General, Dr H. Mahler and his staff , and the Swedish Government, represented by its Director-General for Health Services, Dr Bror Rexhed, and the Director of the Swedish Drug Regulatory Agency, Dr Ake Liljestrand.

9. Conclusion

The road has been long, and the magnitude and results are impressive between the start of the WHO Pilot Research Project in 1968 and the 40th anniversary celebration in 2008 of WHO's International Drug Monitoring, and the 30 years of the UMC. UMC was created in 1978 as a WHO Collaborating Centre when, through agreement with the WHO, the Swedish Government took over the activities and financial responsibilities from the WHO. Some illustrative figures are of interest to demonstrate the scope of development over 40 years: the WHO Pilot Research Project for International Drug Monitoring received 5645 drug reaction reports in 1968 and 18 440 in 1969, from ten countries. In early 2008, UMC reported that they had a total of 4 million case reports, from close to 100 countries. The pilot project had a staff of 12. In 2008, UMC had a staff of 60 full and associate members in Uppsala, and since 2001 it generates its own income through the sale of the Drug Dictionary and other goods and services. (I.R. Edwards, 'Uppsala Reports', April 2002–2008).

Acknowledgements

The authors gratefully acknowledge Dr Myles Stephens for his inspiration and for gently 'pushing' Jan Venulet to write about the early years and history of the WHO International Drug Monitoring.

Jan Venulet and Margaretha Helling-Borda are both WHO retirees, and Margaretha Helling-Borda is a former Director of the WHO Action Programme on Essential Drugs.

Correspondence to: Professor Dr Med. *Jan Venulet*, 15 A Chemin de Bedex, 1226 Thonex, Switzerland.
E-mail: venulet@geneva-link.ch
Margaretha Helling-Borda, Chemin le Grenier 8, 1291 Commugny, Switzerland.
E-mail: m.helling-borda@bluewin.ch

Appendix 1

World Health Assembly Resolutions Reference to ADR from 1962–1970

Fifteenth World Health Assembly, Geneva, 8–25 May 1962

WHA15.41 Clinical and Pharmacological Evaluation of Drugs

The Fifteenth World Health Assembly, considering that:

(1) new pharmaceutical preparations appear in a steadily increasing number on the market;

(2) in many of these preparations a great therapeutic activity may be combined with serious side effects, demanding particular care in administration;
(3) recent experience has shown certain defects in existing safety control measures;
(4) these defects are especially related to insufficient clinical trials;
(5) clinical evaluation represents the final assessment of pharmaceutical preparations and is the principal means of detecting harmful side effects following long term use;
(6) clinical trials are highly time consuming, need very large numbers of patients to be observed according to generally accepted principles, and would often be facilitated by international cooperation;
(7) it should be the responsibility of national health authorities to ensure that the pharmaceutical preparations available to the medical profession are therapeutically efficient and that their potential dangers are fully recognized,

1. REQUESTS the Director-General to pursue, with the assistance of the Advisory Committee on Medical Research, the study of the scientific aspects of the clinical and pharmacological evaluation of pharmaceutical preparations;
2. REQUESTS the Executive Board and the Director-General to study the feasibility or otherwise, on the part of WHO, of:

   (a) establishing minimum basic requirements and recommending standard methods for the clinical and pharmacological evaluation of pharmaceutical preparations;

   (b) securing regular exchange of information on the safety and efficacy of pharmaceutical preparations; and, in particular,

   (c) securing prompt transmission to national health authorities of new information on serious side effects of pharmaceutical preparations, and to report to the Sixteenth World Health Assembly on the progress of this study.

Handb. Res., 6th ed., 1.3 Twelfth Plenary Meeting, 24 May 1962

(section 1 of the seventh report of the Committee on Programme and Budget)

Sixteenth World Health Assembly, Geneva, 7–23 May 1963

WHA16.36 Clinical and Pharmacological Evaluation of Drugs

The Sixteenth World Health Assembly,

Having noted the resolution of the Executive Board on the clinical and pharmacological evaluation of drugs;

Having examined the report by the Director-General on the clinical and pharmacological evaluation of drugs;

Considering that international cooperation is essential for the achievement of the best possible protection against hazards for man arising out of the use of drugs;

Agreeing to the definition of a 'drug' as any substance, or mixture of substances, destined for use in the diagnosis, treatment, mitigation or prevention of disease in man, as set out in the report of the Study Group on the Use of Specifications for Pharmaceutical Preparations;[4]

Realizing the technical and administrative difficulties of securing regular exchange of information on all drugs:

1. REAFFIRMS the need for early action in regard to rapid dissemination of information on adverse drug reactions;
2. REQUESTS Member States
   (a) to communicate immediately to WHO
      (i) any decision to prohibit or limit the availability of a drug already in use
      (ii) any decision to refuse the approval of a new drug
      (iii) any approval for general use of a new drug when accompanied by restrictive provisions, if these decisions are taken as a result of serious adverse reactions; and
   (b) to include in this communication as far as possible the reasons for the action taken and the non-proprietary and other names, and the chemical formula or the definition;
3. RECOGNIZES
   (a) the importance of accurate appraisal, at the national level, of the toxic effects of drugs; and

INVITES

(b) Member States to arrange for a systematic collection of information on serious adverse drug reactions observed during the development of a drug and, in particular, after its release for general use;

4. REQUESTS the Director-General

(a) to transmit immediately to Member States the information received under paragraph 1;

(b) to study the value and feasibility, including the administrative and financial implications, of WHO collecting from and disseminating to Member States:

(i) the non-proprietary and other names, chemical formulae and definitions of new drugs released or approved

(ii) the information contained in 3 (b) above

(c) to continue the study of the possibility of formulating, and of seeking international acceptance of, basic principles and requirements applicable to the toxicological, pharmacological and clinical evaluation of drugs; and

(d) to pursue action in the matter and report to the Executive Board and to the Seventeenth World Health Assembly.

Handb. Res., 6th ed., 1.3 Thirteenth Plenary meeting, 23 May 1963

(Committee on Programme and Budget, fifth report)

Seventeenth World Health Assembly, Geneva, 3–20 March 1964

WHA17.39 Clinical and Pharmacological Evaluation of Drugs

The Seventeenth World Health Assembly,

Having examined the report of the Director-General on the clinical and pharmacological evaluation of drugs;

Having noted resolution EB33.R21 of the Executive Board on the clinical and pharmacological evaluation of drugs;

Desirous of a rapid development of a rational programme by which WHO can contribute to the protection of man against hazards arising out of the medical use of drugs;

Appreciative of the assistance given in this respect by Member States, the Advisory Committee on Medical Research and the Section on Pharmacology of the International Union of Physiological Sciences; and

Convinced that international collaboration and coordination are indispensable for the achievement of such a programme,

1. INVITES all Member States:

(1) to arrange to communicate to WHO any decision to refuse the approval of a new drug, or to withdraw or restrict the availability of a drug already in use as specified in resolution WHA16.36, in so far as they have not already done so, and to ensure that the justification for such action is communicated at the same time;

(2) to develop, as quickly as possible, with a view to eventual international collaboration, their arrangements for the systematic collection and evaluation of information on serious adverse drug reactions observed during the development of drugs and, in particular, after their release for general use; and

(3) to communicate to the Director-General the general principles and requirements which they consider essential for the evaluation of the safety and efficacy of drugs; and

2. REQUESTS the Director-General:

(1) to continue to collect and disseminate decisions relating to adverse drug reactions as specified in resolution WHA16.36 and to report to the Executive Board if and when changes in these arrangements appear desirable;

(2) to pursue, with the assistance of the Advisory Committee on Medical Research, and with a view to eventual international coordination, discussion on satisfactory methods for monitoring adverse reactions, especially late toxic effects, of drugs already in use; and

(3) to undertake, with the assistance of the Advisory Committee on Medical Research, the formulation of generally acceptable principles and requirements for the evaluation of the safety and efficacy of drugs.

Handb. Res., 7th ed., 1.3.2.3 Eleventh Plenary Meeting, 17 March 1964

(Committee on Programme and Budget, fourth report)

Eighteenth World Health Assembly, Geneva, 4–21 May 1965

WHA18.42 Adverse Drug Reaction Monitoring System

The Eighteenth World Health Assembly,

Considering resolutions WHA15.41, WHA16.36 and WHA17.39 of the Fifteenth, Sixteenth and Seventeenth World Health Assemblies on the importance of systematic collection, evaluation, and dissemination of information on adverse drug reactions;

Recalling the reports of the several groups of experts convened to consider and study the feasibility and desirability of instituting an adverse drug reaction monitoring programme on an international basis;

Convinced of the urgent need for the international collection and distribution of information on adverse drug reactions; and

Looking with favour upon the offer of the Government of the United States of America to provide facilities for the processing of information on adverse drug reactions, under the auspices of the World Health Organization,

1. REQUESTS the Director-General to study further the requirements of an international programme for the collection, analysis, and dissemination to Member States of information on adverse drug reactions;
2. INVITES Member States to develop as soon as possible national monitoring systems for adverse drug reactions, with a view to taking part in an international system under the aegis of WHO;
3. REQUESTS the Director-General to examine the offer of the United States of America and of any other governments of data processing facilities as a part of an international monitoring system for adverse drug reactions, and to report on the matter to the Nineteenth World Health Assembly; and
4. THANKS the Government of the United States of America for its offer.

Handb. Res., 7th ed., 1.3.2.3 Twelfth Plenary Meeting, 20 May 1965

(Committee on Programme and Budget, sixth report)

Nineteenth World Health Assembly, Geneva, 3–20 May 1966

WHA19.35 International Monitoring of Adverse Reactions to Drugs

The Nineteenth World Health Assembly,

Having examined the reports of the Director-General on the international monitoring of adverse reactions to drugs;

Recalling resolutions WHA15.41, WHA16.36, WHA17.39 and WHA18.42 of the Fifteenth, Sixteenth, Seventeenth and Eighteenth World Health Assemblies on the importance of systematic collection, evaluation and dissemination of information on adverse reactions to drugs;

Considering resolution EB37.R14 of the Executive Board on the international monitoring of adverse reactions to drugs;

Convinced of the urgent need to collect and disseminate at the international level information on adverse reactions to drugs; and

Taking into account that cooperation with national centres for monitoring adverse reactions to drugs and the utilization of the data processing facilities available in the United States of America would facilitate the international monitoring envisaged,

1. REQUESTS the Director-General to initiate a pilot research project, along the lines indicated in his report, with the aim of establishing an international system of monitoring adverse reactions to drugs using information derived from national centres; and
2. ACCEPTS the generous offer of the Government of the United States of America of data processing facilities for this purpose.

Handb. Res., 8th ed., 1.3.3 Fourteenth Plenary Meeting, 20 May 1966

(Committee on Programme and Budget, fourth report)

Twentieth World Health Assembly, Geneva, 8–26 May 1967

WHA20.51 WHO Pilot Research Project for International Monitoring of Adverse Reactions to Drugs

The Twentieth World Health Assembly,

Having noted the report by the Director-General;[1]

Recalling resolutions WHA18.42 and WHA19.35 on the monitoring of adverse reactions to drugs,

1. NOTES with appreciation the agreement reached between the Organization and the Government of the United States of America concerning a grant for the WHO pilot research project on the modalities of an international system of monitoring adverse reactions to drugs;
2. REQUESTS the Director-General to take the necessary measures for that pilot project to be carried out and to report on its results to the World Health Assembly.

Handb. Res., 8th ed., 1.3.3 Twelfth Plenary Meeting, 25 May 1967

(Committee on Programme and Budget, ninth report)

Twenty-Third World Health Assembly, Geneva, 16 May 1970

WHA23.13 International Monitoring of Adverse Reactions to Drugs

The Twenty-Third World Health Assembly,

Having examined the report of the Director-General on the WHO Pilot Research Project for International Drug Monitoring[1] and the future development of this activity;

Recalling resolutions WHA15.41, WHA16.36, WHA17.39, WHA18.42, WHA19.35 and WHA20.51;

Emphasizing the importance to all Member States of establishing an international system for monitoring adverse reactions to drugs;

Convinced of the urgent need to develop an operational system for the international monitoring of adverse reactions to drugs;

1. NOTES with satisfaction that the pilot phase of the project will shortly have been satisfactorily completed and that voluntary contributions have been pledged which will ensure support for the project until the end of 1970;
2. REITERATES its appreciation to the Government of the Unites States of America for the financial support for the pilot phase and to the other Member States collaborating in that stage of the project;
3. REQUESTS the Director-General to develop the activities of the project into a primary operational phase aimed at the establishment of an international system for monitoring adverse reactions with provision for alerting Member States in cases of urgency in accordance with resolution WHA16.36 and to report to the World Health Assembly;
4. REQUESTS the Director-General to explore the possibility of financing the project from sources other than the regular budget bearing in mind the views expressed in the discussions at the Twenty-third World Health Assembly;
5. DECIDES that subject to (4) above:
   (a) the project shall be financed for 1971 firstly by postponing the addition of $100 000 to the revolving Fund for Teaching and Laboratory Equipment and secondly by withdrawing the balance from the working Capital fund; and that the Director-General be requested to reimburse the working Capital fund up to $US 245 000 from any operational savings that could be effected under the regular budget for 1971;
   (b) provision be made for 1972 and subsequent years for the necessary financing of the project by means of the regular budget;
6. DECIDES that as soon as the necessary arrangements can be made, the project shall be based at WHO Headquarters in Geneva.

Twelfth Plenary Meeting, 16 May 1970
A23/VR/12

Appendix 2

List of References and Selected Background Documents

1. Venulet J. Pilot Research Project for International Drug Monitoring: assignment report by Senior Project Officer, for the period 9 January 1968 to 10 March 1970

1 Documents A23/P&B/7 and A23/P&B/WP/1.

2. Venulet Jan. The WHO Drug Monitoring Programme: the formative years (1968–1975), 13-21, In: Bankowski Z, Dunne J.F., editors. Drug surveillance: international cooperation, past present and future. Proceedings of the XXVIIth CIOMS Conference Geneva, Switzerland, 14-15 September 1993, organized jointly by CIOMS and WHO for the 25th Anniversary of the World Health Organization's Programme for International Drug Monitoring,
3. WHO resolutions: 1962–1970 referring to the topic (see appendix 1 for full texts)
   WHA15.41, 24 May 1962 Clinical and Pharmacological Evaluation of Drugs
   WHA16.36, 23 May 1963 Clinical and Pharmacological Evaluations of Drugs
   WHA17.39, 17 March 1964, Clinical and Pharmacological Evaluation of Drugs
   WHA18.42, 20 May 1965, Adverse Drug Reaction Monitoring
   WHA19.35, 20 May 1966, International Monitoring of Adverse Reactions to Drugs
   WHA20.51, 25 May 1967, WHO Pilot Project for International Drug Monitoring
   WHA23.13, 16 May 1970, International Monitoring of Adverse Reactions to Drugs
4. Nicholas Moore (Professeur de Pharmacologie Clinique , Service Hospitalo, Universitaire de Pharmacologie, Université de Bordeaux, ISOP (International Society of Pharmacovigilance) and Jan Venulet, e-mail correspondence from February 8, 2009, re writing a chapter or two on the earlier periods of pharmacovigilance,
5. WHO Programme founder. Profile of Jan Venulet. Uppsala Reports (UR), April 2003, www.who-umc.org
6. Ahroth E, Aldama A, Christopher L, Helling M, Molander S, and Venulet J. Methodology and some clinical research aspects of the WHO International Drug Monitoring Project. Drug Information Bulletin 1971; 5: 45-48
7. Royall BW, Venulet J. Methodology for international drug monitoring, Meth Inform Med 1972; 11: 75-86
8. Venulet J. O potrzebie systematycznych badan w dziedzinie powikan polekowych, Pol Tyg Lek 1972; 27: 897
9. Venulet J., Adverse reactions to drugs, WHO Research Centre. Int J Clin Pharmacol 1973; 7: 253-264
10. Venulet J. From experimental to social pharmacology (natural history of pharmacology). Int J Clin Pharmacol 1974; 10: 203-205
11. Mach EP, Venulet J. The economics of adverse reactions to drugs. WHO Chronicle 1975; 29: 79-84
12. Helling M, Venulet J. Drug recording and classification by the WHO research centre for international monitoring of adverse reactions to drugs. Meth Inform Med1974; 13: 169-178
13. Helling M. WHO Centre for International Monitoring of Adverse Reactions to Drugs, 29 October 1974 (unpublished document)
14. Venulet J. The need for monitoring ADR (Potreba organiziranog pracenja nuspojava lijekova) Pharmaca (Yougoslavia) 1975; 13: 207-214
15. Mach EP, Venulet J. Counting the costs of adverse drug reactions. Adverse Drug Reaction Bulletin, No. 54, October 1975. Davies DM, editor. Regional Postgraduate Inst For Medicine and Dentistry, Newcastle upon Tyne
16. Venulet J. Increasing threat to man as a result of frequently uncontrolled and widespread use of various drugs, Int J Clin Pharmacol 1975; 12: 387-394
17. Helling M. Experience with the World Health Organization. Chapter 9. In: Gouveia W, Tognoni G, van der Kleijn E, editors. Clinical Pharmacy and Clinical Pharmacology. Amsterdam, New York, Oxford: North Holland Publishing, 1976
18. Venulet J. La pharmacologie social existe-il? Med et Hyg 1976; 34: 435-436
19. Venulet J., Zunehmende Gefährdung des Menchen durch oft unkontrollierte und breitbasige Anwendung verschiedenster Arzneimittel. In: Wannagat L, editor. Toxische Leberschäden. Stuttgart: Georg Thieme Verlag, 1976: 296-304
20. Venulet J, Methods of monitoring adverse reactions to drugs. In: Jucker E, editor. Progress in drug research. Basel and Stuttgart: Birkhàuser Verlag, 1977; 21: 233-292.

21. Venulet J. Aspects of social pharmacology, In: Jucker E, editor. Progress in drug research; 22: 10-25, Basel: Birkhàuser Verlag, 1978
22. Venulet J. Monitoring of adverse drug reactions: the problem of integration of heterogeneous data. Int J Clin Pharmacol 1979; 17: 383-386
23. Helling M, Dunne J. International monitoring of adverse reactions to drugs: reporting, data collection and processing. In: van der Kleijn E, Jonkers JR, editors. Clinical Pharmacy, Elsevier/North Holland and Biomedical Press, 1977: 223-228
24. Helling-Borda M, Mannel P, Mandahl M. Use of computers in drug monitoring. In: Inman WHW, editor. Monitoring for drug safety. 2nd ed. MTP Press Limited, 1986: 305-322,
25. Pharmacovigilance: ensuring the safe use of medicines. Geneva: WHO, October 2004, http://www.who.int
26. The history of pharmacovigilance. In: Talbot J, Waller P, editors. Stephens' detection of new adverse reactions. 5th ed. West Essex: John Wiley & Sons, 2004
27. Edwards R. Reflections on the development of pharmacovigilance. Uppsala Reports (UR), April 2002–October 2008 (UR 18–UR43), www.who-umc.org
28. The safety of medicines: adverse drug reactions, www.who.int
29. Adverse Drug Reactions Monitoring, 2009, www.who.int.
30. "Meeting of minds in Uppsala", 40th anniversary of the WHO Programme for International Drug Monitoring and 30th anniversary of UMC, 2008 meeting in Uppsala. Uppsala Reports 44, January 2009, www.who-umc.org
31. Venning GR. Identification of adverse reactions to new drugs. BMJ 1983; 286; 289-92

Other Useful References: Selected From the Reference List in No. 17 Above: 'Experience with the World Health Organization'

(1) International monitoring: the role of hospital: Wld Hlth Org Tech Rep 1969: Ser 425
(2) International drug monitoring: the role of national centres: Wld Hlth Org Tech Rep 1972: Ser 498
(3) Clinical Pharmacology: scope, organization, training: Wld Hlth Org Tech Rep 1970: Ser 446
(4) Pharmacogenetics: Wld Hlth Org Tech Rep 1973: Ser 524
(5) Bioavailability of drugs principles and problems. Wld Hlth Org Tech Rep 1974: Ser 536
(6) Guidelines for evaluations of drugs for use in man: Wld Hlth Org Tech Rep 1975: Ser 563
(7) Rowland MGM, Stevenson CJ. Exfoliative dermatitis and practolol. Lancet 1972; I: 1130
(8) Felix R. Ive FA. Skin reactions to practolol. BMJ 1972; 2: 333
(9) Anonymous. Practolol: question about adverse reactions. Pharm J 1974; 90
(10) Anonymous. warning on use of sex hormones in pregnancy. FDA Drug Bull 1975; 4
(11) Jasinski DR, Griffith JD, Carr CB. Tilidine (T): morphine- like effects in man. Pharmacologist 1974; 16: 247
(12) Report of the International Conference on Adverse Reactions Reporting System. Washington, DC: National Academy of Sciences, 1971
(13) Doll R. Unwanted effects of drugs. Br Med Bull 1971; 27: 25-31
(14) Feinstein AR. Clinical biostatistics: XXVIII. The biostatistical problems of pharmaceutical surveillance. Clin Pharmacol Ther 1974; 16: 110-123
(15) Finney DJ. Spontaneous reporting of adverse reactions to therapeutic drugs. International Conference on Adverse Reactions Reporting Systems; 1970 Oct 22-23: Washington,
(16) Jick H, Miettinen OS, Shapiro S, et al. Comprehensive drug surveillance. J Am Med Assoc 1970; 213: 9, 1455-1460
(17) Gardner P, Cluff LE. the epidemiology of adverse drug reactions: a review and perspective. Johns Hopkins Med J 1970; 126: 77-87
(18) Vakil BJ, Kulkarni RD, Chabria NL, et al. Intense surveillance of adverse drug

reactions: an analysis of 338 patients. J Clin Pharmacol 1975; 15: 435-441
(19) Friedman GD, Colleen MF, Harris LE, et al. Experience in monitoring drug reactions in outpatients, the Kaiser-Permanente drug monitoring system. J Am Med Assoc 1971; 217: 567-572
(21) Venulet J. Methoden der Uberwaschung und Dokumentation unerwünschter Arzneimittelwirkungen. In: Kuemmerle HP, editor. Methoden der Klinischen Pharmakologie. München; Urban & Schwarzenberg, 1978: 101-132
(22) Proceedings of the Geneva XII International Therapeutic Union Congress, Adverse Drug Reactions. In: Glasson B, Benakis A, editors. Clinical Pharmacology. Génève. Médicine et Hygiene, 1974
(23) Communication from the Danish National Health Service's Board on adverse reactions to drugs: monitoring of adverse reactions to drugs. Ugeskr Laeg 1975; 137: 1270-1272
(24) Coull DC, Crooks J, Davidson JF et al. A method of monitoring drugs for adverse reactions: I. A methyldopa and haemolytic anemia. Eur J Clin Pharmacol 1970; 3: 46-50

Appendix 3

Examples of Some Original 'Information sheets' from the WHO Centre of International Monitoring for Adverse Drug Reactions

WHO Research Centre for International Monitoring of Adverse Reactions to Drugs, 31 January 1975

INFORMATION SHEET NO. 17

Background information concerning the modified version of Report Type H (31 December 1974)

I. Introduction

Adverse reactions to therapeutic drugs are relatively rare events and accordingly, signalling techniques based on the statistics of such events are appropriate.

These techniques are similar to those used in acceptance control sampling and the related control charts. They are based on assumption that the probability of observing a specific event in a given time interval follows the Poisson distribution.

The number of events (drug/adverse reaction combination, or drug alone or adverse reaction alone) reported in each new batch is assessed against the expected number of reports to that event. The latter is estimated from the accumulated number of reports divided by the number of batches from the first time the event was registered.

II. The Main Innovation

Although the presentation of this new printout is largely similar in format to the previous document H on increase in reporting, some important improvements have been incorporated, including more space for country data and a clearer separation of the signalling information from the more general data.

Since the new signalling techniques are based on comparison of the number of reports to a specified event in an incoming batch with the expected number of such reports, and not as before on a comparison of the proportion of reports in the master file and the incoming batch, there is a possibility of an increase ini the number of drugs signalled. Moreover, the addition of system organ class signalling and trend signalling has also led to an increase in the number of signals, in the output.

III. The Statistical Method

In the previous signalling technique we compared the proportion of a given drug/adverse reaction combination in the Master, with that of the batch by the critical ratio test as:

$$\lambda = \frac{|P_B - P_M|}{\sqrt{\sigma_B^2 + \sigma_M^2}}$$

The proposed new statistical system, still in its experimental stage, is based on the comparison of the incoming event with updated expected mean. Taking into consideration that we deal with isolated (or rare) events, and using the unit of time 'K', the batch period for each drug/adverse reaction combination, we obtain

our expected mean as:

$$\tilde{R}_{ME} = \frac{\sum_{i}^{l-1} R_{MX}}{\sum_{i}^{l-1} K_{MX}}$$

Thus, the standard deviation will be the square root of this expected mean. This value will then be compared with the amount of the same specific event coming with the new batch period or KL.

It should be noted that each event has its own characteristic K-value, according to when it was reported for the first time.

$$\sum_{i}^{l-1} K_{MX}$$

The new DEM/RAR (DEM denotes WHO unit of Drug Evaluation and Monitoring and RAR denotes Research Centre for International Monitoring for Adverse Reactions to Drugs) signalling function is called 'Delta', to distinguish it from the previous one designated 'Lambda', and can be written as:

$$\delta = \frac{R_{BL} - \tilde{R}_{ME}}{\sqrt{\tilde{R}_{ME}}}$$

where R_{BL} = number of reports to the specified event in the last incoming batch, KL and R_{ME} = the expected (mean) number of reports to that event, based on the accumulated number of reports in the master file divided by the number of K for that event.

For the time being, the threshold values for generating a signal have been maintained at the same levels, i.e. 1.28 for moderate to severe reactions, and 2.58 for minor reactions.

The calculations performed so far, using the new signalling function 'Delta', have suggested that it yields, in general, higher signal values than does the signal based on Lambda, which was being used previously. In addition, since the Delta function focuses on each specified event, without reference to other drugs or adverse reactions, the possibility of signalling more events increases accordingly.

In order to reduce this increased number of signals generated, a threshold value of at least ten reports to any event has been adopted before that event is signalled.

Even with this restriction, those drugs that are widely used or that have been reported over a long period of time tend to produce a large number of signals; these signals do not necessarily suggest that there has been a real increase in reporting. In such cases, most of the signals generated to the same drug tend to indicate same or similar adverse reactions all the time. This suggests that these signals would be mainly due to an increase in the use of the drug in question. Examples of this situation are the signals generated by acetylsalicylic acid and ampicillin in the December 1974 issue of Document Type H.

If the National Centres require more detailed information, this can be provided on request from the WHO Centre.

The last part of the printout, presenting the 'residual' signals arising from system organ classes and adverse reactions without reference to any specific drug, has been suppressed in this publication. These signals can, however, be provided to anyone interested, on request to the WHO Centre.

Your comments, concerning the new version of the Report Type H, will be most welcome.

WHO Research Centre for International Monitoring of Adverse Reactions to Drugs, 7 February 1975

INFORMATION SHEET NO. 18

What to report: News from Sweden

We have translated and abstracted an article published in Svensk Farmaceutisk Tidskrift, Vol. 79, No.1, page 4, where new instructions on what type of adverse reactions should be reported are communicated to doctors.

''On the first of January 1975 the instructions to doctors for the reporting of adverse drug reactions will change. Until now the Department of Drugs has recommended that doctors report adverse reactions, but from 1 January 1975 doctors are required to report adverse reactions observed. Already the suspicion of an adverse reaction should be reported. Distinction is no longer made between old and new drugs.

Adverse reaction reporting, on a trial basis, started in 1965, and became permanent from January 1971. The collecting, preparation and

evaluation of reports has been carried out by the Adverse Reaction Section in the Department of Drugs and by the Adverse Reaction Committee.

From 1 January 1975 doctors and dentists have to report:

(a) All deaths suspected of being caused by drugs;
(b) All serious reactions, i.e. those not causing death, but having a considerable influence on the patient's general condition, the course of the disease and the length of stay in hospital; and
(c) All new and unexpected reactions or any other reactions that the doctor considers worthwhile reporting.

Doctors and dentists are free to report other types of reactions. In the circular from the Social Board of Health and Welfare (Socialstyrelsen) it is stressed that it is of value to report reactions of increasing frequency, regardless of whether they are considered serious or not. Increase in frequency can be a sign of widespread sensitization, new interactions, changes in the quality of a drug, etc.

In an article in the Swedish Medical Journal, No. 51 (Läkartidningen), Professor Lars-Erik Böttiger says he is expecting an increased number of reactions. This is not due to an increased number of drugs but to the fact that now there exists more highly effective drugs, with very specific target areas. This requires exact diagnosis and knowledge of treatment. For many of the highly effective and pure preparations, the margin of safety seems to be very small, exemplified by the documented increase of digitalis toxicity.

If a drug is suspected of producing an adverse drug reaction, the material is later evaluated by the Adverse Reaction Committee in three steps:

(1) by the medical officer in charge (komitténs verkställande ledamot)
(2) by the working group (three doctors)
(3) by the Committee.

Böttiger emphasizes that the aim is not to establish an absolute or legally enforced cause-relationship for each individual case, but rather to measure the statistical probability on which recommendations could later be based."

Appendix 4

Example(s) of Drug Comments from the WHO Centre of International Monitoring for Adverse Drug Reactions, 1973, 1974 and 1975

Warning System

Introduction

Even with the comparatively small number of adverse drug reaction reports in the early 1970s, problems were identified, and confirmed that data from different places could lead to early recognition by actions taken by different national centres.

The signalling system created at the central place, the WHO Centre for International Monitoring of Adverse Drug Reactions, led to analysis and dissemination of drug comments from the Centre; as visualized by the objectives of the pilot phase, thus strengthening the concept of operating an early warning system for adverse drug reactions.

***Example of Drug Comment from the Centre*:**

DRUG COMMENT No. 34 DATE 17 MAY 1973

DRUG: ERYTHROMYCIN REVIEWED BY: SWEDEN

SIGNALLED IN REPORT TYPE H, No. 21, March 1973

Erythromycin base is a metabolic product of streptomycin erythreus. It is named a macrolide antibiotic because of the large lactone ring in the structure. Erythromycin base is adequately absorbed from the upper part of the small intestine. Activity is destroyed by gastric juice and food in the stomach delays its ultimate absorption. To overcome this, the drug has been manufactured in capsules with an acid-resistant coating or administered as erythromycin stearate.

Erythromycin estolate, the lauryl sulphate of propionic acid ester of erythromycin, is less susceptible to acid decomposition than the parent compound. It retains its potency at the pH of gastric juice for prolonged periods and is absorbed to a larger degree than the other forms of the drug. Erythromycin base, erythromycin stearate and erythromycin estolate are the most

used oral preparations. Erythromycin ethylsuccinate is the most used parenteral preparation.

Depending of the nature of the organism and the concentration, erythromycin may be bacterostatic or bacteriocidal. It is most effective against Gram-positive bacteria. Examples of sensitive microorganisms are *Streptococceus aureus, Hemolytic streptococcus* group A, Pneumococcus, *Clostridium*, *Neisseria*, *H. influenza B*, pertussis, *Entamoeba histolyticum* and *Mycoplasma pneumoniae*.

The incidence of untoward effects with erythromycin is fairly low. Among hypersensitivity reactions are fever, eosinophilia and skin eruptions. Gastrointestinal discomfort after oral administration has also been reported.

Experimental studies have shown that a reversible myasthenic-like picture was obtained during erythromycin administration. This may explain complaints of general weakness presented by patients receiving treatment with such antibiotics.

Erythromycin estolate has long been known to cause reversible cholestatic hepatitis. It starts after about 10 to 20 days of treatment and is characterized early by abdominal cramps often mimicking acute cholecystitis and nausea or vomiting. These are followed shortly by jaundice, fever, leukocytosis, eosinophilia, elevated plasma transaminases and bilirubin levels; the cholecystogram is negative. The clinical and pathological findings are very similar to those observed with the hepatic disturbances produced by chlorpromazine. Patients with liver disturbances should not receive erythromycin estolate. Patients who have developed hepatotoxicity while under treatment with erythromycin estolate have recovered after this drug was replaced by erythromycin stearate.

Hepatotoxicity from erythromycin estolate may be secondary to a hypersensitive mechanism. It is of relatively rare occurrence and may be accompanied by rash, fever and eosinophelia. The intrahepatic cholestasis has been related to alterations of the canalicular membrane of the liver cells. Present data suggest the possibility that drug-induced organic damage in immunologically sensitive patients might also require some direct hepatotoxic actions of the drugs involved. This in turn might partially explain why not all hypersensitivity drug reactions are accompanied by obvious signs of cellular injury.

References

Goodman and Gilman. The pharmacological basis of therapeutics, 3rd edition

Kendler, Anuras, Laborda and Zimmerman. Perfusion of the isolated rat liver with erythromycin estolate and other derivatives. Proceedings of the Society for Experimental Biology and Medicine 1972. 139: 1272-1275.

Herishanu and Taustein. The electromyographic changes induced by antibiotics: a preliminary study. Confin Neurol 1971; 33: 41-45

McLeavey and Beveridge. Clinical trial and erythromycin stearate suspension. Med J Aust 1971: 793-796

Dujovne, Shoeman, Bianchine and Lasagna. Experimental bases for the different hepatotoxicity of erythromycin preparations in man. J Lab Clin Med 1972: 834-844

***Example of Drug Comment from the Centre*:**
DRUG COMMENT No. 50
DATE 12 SEPTEMBER 1974
DRUG: TILIDINE[2]
REVIEWED BY: THE WHO CENTRE
SIGNALLED IN REPORT TYPE L, No. 8, September 1973

After the note in Information Sheet No. 10 dated 3 December 1973 and following the suggestion of the March 1974 Consultation on Approaches for Detection of Adverse Reactions to Drugs at an Early Stage, complete data is provided in the form of this comment and as additional information from the Addiction Research Center in Lexington, Kentucky, USA.

From tabulated case material presented during the meeting, it has been concluded that

2 Tilidine is the International Nonproprietary Name (INN) proposed by WHO for Ethyl 2- (dimethylamino)-1-phenyl-3-cyclohexene-carboxylate. In FRG (Federal Republic of Germany) it is marketed under the trade name of Valoron as the hydrochloride.

tilidine shows a use pattern of drug dependence. Either the development of tolerance of drug-seeking behavior, 'hustling' or the appearance of a withdrawal syndrome after reduction of doses, between doses or during enforced abstinence, is present to a variable degree in all patients. Doses are increased excessively and reach, in a few cases, 14, 40, 45 and 60 units per day. Tilidine is available in both oral and parenteral forms in 50 mg dosage units. Four to eight single dosage units daily are recommended to obtain effective analgesia.

It was stated at the meeting that "the development of drug dependence in patients who may have had prior experience with narcotic analgesics could indicate that abuse can become a problem in individuals who may not have prior history of drug addiction".

Experiments now conducted have shown that morphine-like subjective effects and miosis can be produced by tilidine in non-dependent subjects. Also abstinence in morphine-dependent subjects can be suppressed by tilidine. These investigations employed both the subcutaneous and oral routes of administration. Tilidine is shown to be a morphine-like agent, more active orally than parenterally. However, parenteral potency of about one half the oral activity makes illicit intravenous abuse a possible reality, if solubility is no problem. In addition, the dangers of addiction exist in patients who have justifiable needs for an oral analgesic.

The combined experience with tilidine from the case reports in the international monitoring of adverse reactions to drugs and from the follow-up experiments at the Addiction Research Center in Lexington, Kentucky, suggest that tilidine, pending further evaluation, should be considered a narcotic. All the consequences of what such a designation implies should be kept in mind by those who follow this new analgesic, either during its introductory period on the market, or while it is still under investigation.

References

1. Herman M, Steinbrecher W, Heldt W. Arzneitmittel-Forsch 1970; 20: 977-983
2. Bulletin. Problems in Drug Dependence 1970; Addendum. 1: 10, 14-15
3. Tilidine (T): morphine-like effects in man. The Pharmacologist 1974; 16: 247

