SESSION III

HARMONIZATION OF REPORTING AND TERMINOLOGIES OF ADVERSE DRUG REACTIONS

Chairman: Ronald D. Mann

HARMONIZATION OF REPORTING AND TERMINOLOGIES OF ADVERSE DRUG REACTIONS

Introduction

Ronald D. Mann*

There are three principal issues involved in the harmonization of reporting requirements and the provision of suitable terminologies relating to reporting of adverse drug reactions. These are:

1) The reporting requirements of drug regulatory agencies.
2) Classification systems by which ADR reports can be computerized.
3) Nomenclatures or dictionaries defining adverse-drug-reaction reporting terms.

1. Reporting requirements

There has, in the past, been great difficulty because individual national drug regulatory agencies and governments have put forward rules and regulations for reporting of adverse drug reactions, and these requirements are not harmonized. Each drug regulatory body tends to disseminate rules and regulations of its own and this leads to pharmaceutical companies having to report precisely the same information in a number of different formats. This duplicative and entirely unnecessary work risks erosion of the data-base through multiple reporting. It is also wasteful of resources and it does nothing to enhance patient-care, which is the prime object of adverse drug reaction reporting.

It is essential that we work towards international agreements regarding reporting requirements, and useful steps in this direction have been made by the CIOMS I and II agreements. Further work is in progress in the CIOMS III working group.

The CIOMS I agreement was concerned with the international reporting of adverse drug reactions. It did not interfere with national reporting requirements, but ensured that there would be one form, with one set of definitions, to be completed in one language for international reporting. The idea was that drug regulatory agencies could define their reporting requirements as they wished for use within their own countries, but pharmaceutical companies, which had to undertake international reporting, would do this by means of the CIOMS I form and procedure.

The CIOMS II agreement is concerned with periodic safety updates. Many regulatory authorities require that, from time to time, pharma-

* Drug Safety Research Unit, Southampton, UK

ceutical companies should provide a summary of the adverse reaction experience which had occurred since the date of the last report. These requirements also vary from one regulatory body to another, and the CIOMS II agreement provided a format allowing one unified report which could be sent to all regulatory authorities that were willing to participate in the scheme.

There remain a number of current needs:

(a) It is necessary to increase the number of countries and pharmaceutical companies that use the CIOMS I and II procedures. It also seems perfectly sensible to use the same procedures for internal reporting within individual countries, and further consideration needs to be given to this possibility. Certainly it is desirable to bring national reporting requirements into some sort of uniformity.

(b) It is necessary to make sure that countries setting up drug regulatory authorities should have the CIOMS I and II agreements drawn to their attention so that they can seriously consider participating in these schemes from the beginning. This will apply particularly to Eastern European countries and developing countries, and their adoption of the CIOMS I and II procedures would avoid their generating independent and non-harmonized regulations.

(c) It is necessary to differentiate validated from non-validated reports. Data quality is important and we do need to evolve a means of showing which reports have been validated by further follow-up and can therefore be accepted as authenticated.

(d) It is also desirable to indicate reports for which biological samples have been stored. As we move towards increasing capability regarding phenotyping and genotyping, the usefulness of storing biological samples for subsequent examination increases. Central adverse-drug-reaction registers should record which reports have been handled in this way.

(e) It seems clearly necessary to develop the World Health Organization's international drug safety monitoring data-base at Uppsala. This will avoid the setting up of unnecessary data-bases in the European Community and elsewhere. It seems very difficult to justify duplicative data-bases in scientific terms and this matter would seem to be of some importance.

2. Classification systems

There are clear advantages in using a classification system. These include:

(a) Data can be recorded more quickly and more accurately.
(b) Data can be retrieved far more easily.
(c) Data can be analysed far more thoroughly.
(d) Data can be communicated more regularly in a standardized form.

There are a number of different classification systems in extensive use; they include ICD (International Classification of Diseases) 8/9/10, OXMIS, READ, ADROIT, WHOART and COSTART.

The first part of Volume 1 of the ICD ninth revision provides a list of three-digit categories. The bulk of the volume then goes on to expand this classification in terms of four-digit sub-categories. The ICD classifications are in widespread use and are considered by most workers to be indispensable. They would seem to be at their strongest in classifying diseases rather than symptoms and less well defined clinical conditions.

The OXMIS problem codes are based on the International Classification of Diseases (8th Revision) and the Classification of Surgical Operations (1975) of the Office of Population Censuses and Surveys in the United Kingdom. Entries are cross-referenced, where possible, to the disease coding system of the Royal College of General Practitioners (RCGP) and the International Classification of Health Problems in Primary Care (ICHPPC) of the World Organization of National Colleges, Academies and Academic Associations of General Practitioners and Family Physicians (WONCA). The system, which is currently in use on the VAMP database in the United Kingdom, links the RCGP WONCA/ICHPCC Codes to a series of unique numerical and alphabetical identifiers which provide codes for the clinical conditions listed. The system is non-hierarchical, but is extremely useful in the hands of general practitioners because it permits the easy recording of symptoms and less well-defined clinical conditions.

The READ clinical classification became Crown copyright in the United Kingdom in April 1990 when the National Health Service Centre for Coding and Classification was established to develop the READ codes for use throughout the British National Health Service.

Unlike OXMIS, the READ Classification System is hierarchical in structure; it is also capable of considerable extension as the need arises to add further codes. The dictionary itself comprises the Read code (the main or "preferred" medical terms — that is, the nomenclature) and "synonyms", which are linked to the preferred terms. Care is needed to ensure that such systems do not force data entries so that they receive a somewhat erroneous specificity or precision — it is important that if the doctor wishes to record an incident as having been a "heart attack" then this is not forced into the rather more precise and well-defined condition of "myocardial infarction".

ADROIT is a classification system developed by the Medicines Control Agency of the Department of Health in the United Kingdom and intended to provide, on a hierarchical basis, a composite and all-embracing classification system which embodies the codes of many other systems. It has not yet received usage outside the UK and few details are available in the scientific literature.

WHOART and COSTART are the hierarchical classification systems brought forward and used for a considerable number of years in the World Health Organization's international reporting scheme and, in respect of COSTART, in the offices of the Food and Drug Administration in the United States. Those concerned are considering the possibility of linking or uniting these very important systems and updating them.

3. Dictionaries

Having accurate definitions of individual reporting terms is clearly essential if classifications of these terms are to mean anything and if data from different sources are to be recorded on the same data-base. At least two initiatives have been undertaken in attempts to secure internationally acceptable definitions of terms used in reporting adverse drug reactions. One is being led by Dr Christian Bénichou, who has organized a number of meetings which have proposed definitions of terms in a series of publications put forward in France. Bénichou's group has also produced, in English, a series of definitions covering liver problems and blood dyscrasias. The second initiative under the auspices of CIOMS has taken place under the chairmanship of Dr Mann. It has been sponsored by seven German and three Swiss pharmaceutical companies. This effort started with a 1980 list of critical terms and has developed a standard format in which each term is treated by means of a "preamble", a "definition" and "basic requirements for use of the term". The definition is intended to provide a description which will be useful to those validating reports of adverse drug reactions. The preamble sets forth a short list of the specific points that should be borne in mind in determining whether a report satisfies a definition. The section on basic requirements is also intended to facilitate validation listing points of special relevance to the definition. This initiative is continuing and is now beginning to define the terms used in the system-organ classifications of WHOART.

The terms which have recently been defined by the CIOMS group of workers have been published in a series of four papers in *Pharmacoepidemiology in Drug Safety*. The terms defined are the following:

I *Anaphylactic shock, arrhythmia, cardiac failure, hypertension, thrombosis, embolism.*

II *Colitis, gastrointestinal haemorrhage, hepatocellular damage, peptic ulcer, pancreatitis.*

III *Aplastic anaemia. bone marrow depression, coagulation disorders, agranulocytosis, thrombophlebitis.*

IV *Dyskinesia, depression, myopathy, neuropathy, paralysis, convulsions.*

TOWARDS A DICTIONARY OF ADVERSE DRUG REACTIONS OR SHOULD EXISTING TERMINOLOGIES BE HARMONIZED?

Christian Bénichou*

It seems timely and even crucial to turn our attention to the need for one universal worldwide terminology for adverse drug reactions. This is essential to allow exchange of information between the different parties involved in drug safety within the same country and between different countries. Indeed, owing to cultural or nosological differences, terms apparently very close to one another may be applied to different situations. For instance, the French term *thrombophlébite* applies to any venous disorder associating thrombosis and inflammation, including deep vein thrombosis, while the English term *thrombophlebitis* designates superficial phlebitis. Worldwide data-banks centralizing information from many countries are the best way to accelerate knowledge on the safety of new drugs. But this centralization can be effective only if the same terms are used for the same disorders. A few adverse-reaction terminologies have been proposed, such as WHOART and COSTART. None has been associated with definitions or precise guidelines for the use of the terms. Therefore, it is impossible to be sure that each user always uses the same term for the same abnormality. This reservation applies to those using the terminologies in a central data bank as well as to the notifying reporters who originate the information. Thus a dictionary with definitions of all terms or guidelines for their use could be the solution to ensuring that different users "speak the same language".

The nature of adverse drug reactions is not very different from that of the non-drug-induced diseases, except for a very few uncommon and well-known reactions, e.g., fixed drug eruption. Therefore, theoretically the definitions given by medical dictionaries of diseases should suffice. However, at least three main reservations must be made:

- Definitions given by different medical dictionaries are not always concordant and not all dictionaries take into account variations related to age, sex or ethnic origin.
- Dictionary definitions are not always usable in practice and are not adapted to the level of information contained in spontaneous notifications reporting adverse drug reactions attributed to marketed drugs. Histological, biochemical or virological data are rarely available.
- Most ADR terms refer not to diseases but to physical signs, which much more than diseases need precise definitions, not often found in dictionaries.

* Drug Monitoring Department, Roussel Uclaf, Paris, France

To solve these three problems, it would be necessary to create an international dictionary of adverse drug reactions, giving definitions precise enough to reduce to a minimum the risk of wrong assignation to a term. A margin of error is inevitable since the information is usually not sufficient to assure 100% specificity and sensitivity. Such a dictionary of adverse reactions should be constructed in such a way as to take into account up-to-date knowledge about non-drug-induced diseases — that is, with the help of experts from each medical field. Such a project could appear extremely ambitious: how many years would be needed to rethink completely a medical dictionary, universally accepted and adapted to drug safety? The work is probably not insurmountable, since it is a question of redefining not all diseases, but only those likely to be induced by drugs. Moreover, certain system organs are more frequent targets of drug toxicity, such as the liver, blood, skin and kidney, and should be dealt with as top priorities. In each medical field lists should be drawn up of abnormal conditions liable to be induced by drugs. One term should correspond to one condition, and the different terms retained should correspond to different conditions. All the conditions likely to be encountered should be anticipated in the list of terms. To sum up the two essentials for a terminology:

1. For each condition, one term
2. When two different terms are retained, they should correspond to conditions that have a significant clinical difference for the patient — that is, involving different seriousness, prognoses and risks.

Experience shows that all languages have several terms to designate the same condition, or conditions that are not very different. The criterion for a good terminology is to retain only the terms that deserve to be included. It is possible, however, to give for each of these terms a list of synonyms (or included terms). But outdated terms from the past, representing physiopathological or nosological conceptions no longer accepted, must be progressively eliminated from current use.

Knowing that an ADR dictionary cannot be built without the support of experts from the different medical fields, we organized consensus meetings for definitions and causality — assessment criteria of ADRs, gathering university experts in the principal domains of medical toxicity, and specialists in pharmacovigilance from industry and regulatory authorities. This effort was carried out first in France, and then, at the request of the Council for International Organizations of Medical Sciences, at the international level. All of the conclusions have been published (1-10). The international meetings covered liver disorders and blood cytopenias. For liver disorders, experts came from six different countries. First they listed the specific abnormalities which enable the existence of an hepatic disorder to be verified. Then they proposed a classification of these abnormalities into several categories. They proposed a new ratio which facilitates the distinction between hepatocellular and cholestatic injuries (Table 1). And, finally,

they made comments on the different terms retained by WHOART for the system organ: liver and biliary tract disorders.

Table 1. Designations of drug-induced liver disorders on basis of abnormalities shown by liver tests

Terms requiring histological data:	*Type of liver injury:*
Hepatitis	Hepatocellular: increase of over 2N in ALT alone, or $R \geqslant 5$
Hepatic necrosis	Cholestatic: increase of over 2N in AP alone, or $R \leqslant 2$
Chronic liver disease	Mixed: increase of both ALT over 2N and AP, and $2<R<5$
Cirrhosis	Acute: elevation of liver tests lasting less than three months
In the absence of histological data:	
Abnormalities of liver tests: • any increase between N and 2N in – ALT – or AST – or AP – or TB	Chronic: elevation of liver tests lasting more than three months Fulminant: rapid (days to weeks) development of hepatic encephalopathy and severe coagulation disorders
Liver injury: • increase over 2N in ALT or CB • or combined increase in AST, AP and TB, providing one of them is above 2N	Severe: liver injury complicated by, in order of increasing severity: jaundice, prothrombin <50%, hepatic encephalopathy.

Symbols: ALT = Alanine aminotransferase; AST = Aspartate aminotransferase; N = Upper limit of the normal range; AP= Alkaline phosphatase; CB = Conjugated bilirubin; TB = Total bilirubin.

$$R \text{ (ratio)} = \frac{\text{Serum activity of ALT}}{\text{Serum activity of AP}}$$

(Each activity is expressed as a multiple of N. Both should be measured together at the time of recognition of liver injury.)

From the initial set of definitions it was possible to draw up recommendations for the use of all of these terms. Later, in collaboration with the WHO Collaborating Centre for International Drug Monitoring at Uppsala, it was possible to work on what could be a new terminology of adverse drug reactions, cleared of obsolete terms, enriched with new terms which the evaluation of drug effects and progress in knowledge had justified adding, and always accompanied by practical definitions or recommendations for use. Then the

definitions were submitted to different countries, collaborating with WHO, and their comments were taken into account. It has now been offered for publication as a trial example for general opinion. The conclusions of the international consensus meeting (9), published four years ago, did not produce any fundamental criticism and are widely used. If this holds true for this first chapter of a new dictionary, it may be concluded that it fulfils the conditions necessary for a world-wide standardized terminology.

This standardization will probably make unnecessary the harmonization so often called for between the different terminologies. Harmonization could only be accomplished by passing through an initial phase of definition in order to verify the equivalences between the terms of the different terminologies. It will be superfluous if the dictionary is well constructed, since it should be sufficient to attach to each term the different synonyms existing in each terminology. Obsolete terms should be eliminated from current use. New terms should be added. Finally, certain terms may be assembled in larger entities, allowing regrouping of common mechanisms to investigate certain conditions of drug toxicity.

Therefore, the war between terminologies should not take place: the dictionary of adverse reactions, drawn up with the help of international experts and adapted in accordance with the comments of specialists in pharmacovigilance, should make harmonization of the various terminologies unnecessary.

References

1. Bénichou C, Danan G, Lack of definitions of adverse drug reactions. *Drug Inform J.* 1989; **23**: 7174.
2. Danan G, Consensus meeting on causality assessment of drug-induced liver injury. *J. Hepatol* 1988; **7**: 132-136.
3. Solal Céligny P, Bénichou C, Boivin P, et al. Critères d'imputation d'une cytopénie granuleuse ou plaquettaire à un médicament. Résultats de réunions de consensus. *Nouv Rev Fr Hematol* 1987; **29**: 265-270.
4. Habibi B, Solal Céligny P, Bénichou C, et al. Anémies hémolytiques d'origine médicamenteuse. Résultats de réunions de consensus. *Therapie* 1988; **43**: 117-120.
5. Vigeral P, Baumelou A, Bénichou C, et al. Les insuffisances rénales d'origine médicamenteuse. Résultats de réunions de consensus. *Nephrologie* 1989; **10**: 157-161.
6. Fournier M, Camus P, Bénichou C, et al. Pneumopathies interstitielles. Critères d'imputation à un médicament. Résultats de réunions de consensus. *Press Med* 1989; **18**: 1333-1336.
7. Guillaume JC, Roujeau JC, Chevrant-Breton J, et al. Comment imputer un accident cutané à un médicament. Application aux purpuras vasculaires. *Ann Dermatol Venereol* 1987; **114**: 721-724.
8. Roujeau JC, Béani JC, Dubertret L, et al. Photosensibilité cutanée médicamenteuse. Résultats d'une réunion de consensus. *Therapie* 1989; **44**: 223-227.
9. International Consensus Meeting. Criteria of drug-induced liver disorders. *J Hepatol 1990;* **11**: 272-276.
10. Bénichou C, Solal Céligny P, Standardization of definitions and criteria for causality assessment of adverse drug reactions. Drug-induced blood cytopenias. Report of an International Consensus Meeting. *Nouv Rev Fr Hematol* 1991; **33**: 257-262.

THE THREE CIOMS WORKING GROUPS ON DRUG SAFETY

Win M. Castle* and Diane Chen**

This paper describes how the Council for International Organizations of Medical Sciences (CIOMS) became involved in the three working groups on drug safety: the first on expedited case reports; the second on the periodic safety review of drugs; and the third on safety elements in core data sheets.

The beginning

The working parties originated from a CIOMS working group in 1985 on the monitoring and assessment of adverse drug effects. One of its purposes was to make proposals for the reporting of adverse drug reactions, with particular reference to the needs of developing countries. However, it became evident that even among the more developed countries, such as the Federal Republic of Germany, the United Kingdom and the United States, with reasonably efficient systems, there was disharmony in international reporting, and manufacturers were concentrating on paper-flow instead of following up important case reports.

Not only were the requirements different between countries, but the items of information required by the regulatory authorities differed markedly. Table 1 (Annex) shows 14 items of information required at that time by the regulatory authorities of the Federal Republic of Germany (BGA), the United Kingdom (MCA), and the United States (FDA), and this was only a third of the information which was required by any of them.

Therefore, a decision was made to convene a group of interested people from regulatory agencies and the pharmaceutical industry, as well as observers from the World Health Organization, to discuss the feasibility of standardizing international reporting of adverse drug reactions. They were invited by either Dr Gerry Faisch (FDA) or Dr Win Castle (ICI) to attend a week-end meeting. Their selection was arbitrary; nobody was officially representing any organization. They agreed on the following: the definition of a reportable individual reaction; the data elements which should be in the report, and a procedure and format for submitting the same report to all interested regulatory authorities. So that the initiative and the consensus reached would not be wasted, Dr Bankowski suggested that the group become

* International Drug Surveillance, Glaxo Research Institute, Research Triangle Park, NC 27709, USA

** CKW Consulting, Gloucester, Massachusetts 01930, USA

the first CIOMS working group on international reporting of adverse drug reactions. At each subsequent meeting from 1987 through 1989 the group reviewed its set of agreements and procedures and examined progress.

CIOMS I — Expedited case reporting

The agreements reached

- Reports were to be submitted by all manufacturers to all regulatory bodies on the same prescribed CIOMS form (Figure 1, Annex).
- Local reporting requirements would be unchanged.
- Cases requiring international reporting were defined as those which were serious, medically substantiated, and unlabelled (in the product core data sheet), and which occurred in patients in foreign countries. In addition, the reports should be reactions and not events — i.e., the physician or other health-care professional had judged with a reasonable possibility that an observed clinical occurrence had been caused by a drug. The working group took the view that all spontaneous reports were of suspected reactions, otherwise they would not be reported. In clinical trials the physician had the responsibility of identifying those which were "possibly" or likely to be drug-related.
- There had to be a minimum standard of information before the case was reported: an identifiable source, a patient (even if not precisely identified by name and date of birth); a suspect drug and a suspect reaction. If any of these essential elements was missing, no report needed to be submitted until the missing information had been obtained through follow-up inquiries. However, it was essential that manufacturers made genuine efforts to follow up reports of a possibly serious nature.
- The reports had to be sent no later than 15 working days after being identified as "CIOMS reportable".

A retrospective look at CIOMS I

The CIOMS I agreement was remarkably successful and the drug regulatory authorities of the United Kingdom, Italy and Germany have incorporated CIOMS I reports in their regulations. Although the FDA in the United States is now changing the format of its internal domestic reports in its MEDWATCH initiative, it is agreeing to accept CIOMS I reports for overseas cases, and all regulatory authorities requiring expedited overseas reports accept them. Nevertheless, the CIOMS working party is not complacent and is anticipating the time when the information will be sent from the manufacturer electronically, instead of by hard copy, through regulatory authorities' databases to WHO.

Several factors contributed to the success of the working group. Firstly, its relatively small size encouraged open dialogue. Secondly, all

members were encouraged not to focus on their own organizations but to strive for a consensus view. Having reached consensus, members agreed to accept responsibility for trying to put the agreement into effect both within their organizations and elsewhere. Finally, CIOMS working groups are, as the name indicates, working groups, not debating societies. Nowhere was this more true than in the CIOMS second working group.

The CIOMS II Working Group — International reporting of periodic drug-safety update summaries

CIOMS Working Group I had focused on reports of adverse drug reactions occurring in countries other than the country of the particular local national regulatory authority, but regulatory authorities also require safety updates, based on both domestic and foreign data, and this was the subject of CIOMS Working Group II. A safety update is an interim report and by its nature is not an alert. Rather, it should review information accumulated from various sources since the previous report and put it into context against previous information. As with CIOMS I, it was the aim of CIOMS II that each regulator requiring a periodic safety report would receive the same update at the same time. Any new important safety issues should continue to be brought immediately to the attention of prescribing physicians through the regulatory authorities, according to current procedures.

Background

Just as the first CIOMS Working Group had been motivated to try to harmonize the various regulatory requirements, the second CIOMS Working Group also tried to harmonize the multitude of requirements for periodic safety updates, as shown in Tables 2 and 3 (Annex). Work began in Amsterdam towards the end of 1989, and by the middle of 1990 the working group had proposals for the content and format of the periodic updates. At the 1990 October meeting, it was agreed that all representatives from industry would follow the draft CIOMS II proposals and compile a pilot safety-data-update for at least one drug. Each update would then be circulated individually to the regulators in the working group for review. The evaluation of the pilot safety update reports followed largely the formats suggested by Dr Hugh Tilson.

By the middle of 1991 and on the basis of the results of the manufacturers' ten prototypes, the proposals for periodic safety updates were clarified, refined, and agreed. A draft report was prepared describing the proposals, and a mock-up prototype written by Mrs Sue Roden of Glaxo was included. The lesson learned from the pilot project was to balance brevity and reader-friendliness whilst ensuring that the information was sufficient to enable regulators to fulfil their public health role of monitoring drug safety. The group

regards the final CIOMS II proposals as a practical, achievable, standardized format for meeting these goals.

CIOMS II proposals

The CIOMS II Safety Update contains nine items:

- The brief *introduction* is to ensure that the reviewer cannot misinterpret the scope of the report.
- The *core data sheet* is a document prepared by the manufacturer, containing all relevant safety information, such as adverse drug reactions, which the manufacturer stipulates should be included in all countries where the drug is marketed. It is the reference document by which "labelled" and "unlabelled" are determined internationally for CIOMS I reports.
- The *drug's licenced status for marketing* describes the number of countries where the drug is approved and marketed.
- The *update of regulatory* or *manufacturer actions taken for safety reasons* should include descriptions of any drug licence suspensions, restrictions on distribution, or any clinical trial programmes leading to significant alterations in label or package insert, such as lowering of the recommended dosage, for safety reasons. There should be a brief narrative stating the reasons for any significant regulatory or manufacturer action.
- *Patient exposure* is not always easy to ascertain, but the manufacturer is obligated to give the best estimate possible and describe the method used for its estimate.
- *Individual case histories* are presented in the safety updates on one line each as a line listing. For clinical trials the unlabelled serious adverse reactions that are required as expedited reports according to the CIOMS I criteria are included. For spontaneous reports, the CIOMS I criteria were expanded to permit all serious (i.e., labelled and unlabelled) cases to be included on the line listing as well as non-serious unlabelled cases. Consumer reports that cannot be medically confirmed but considered relevant by a medical professional in the industry and published individual case histories should be included. Although reports from regulatory authorities to the manufacturer were not specifically required in the original CIOMS II line listing, subsequent experience has shown that these are useful. CIOMS line listings of case reports require all relevant cases to be presented in body-system order, giving the country, source (e.g., study/prescribing physician), the age and sex of the patient, dose of the drug, duration of treatment prior to the event, the time to onset, the description of the reaction as reported, the outcome (e.g., fatal/resolved), and any comments that the company wishes to make, as well as the case's company reference number in case a regulator wants more information on a particular patient.

- A section on *studies* includes newly analysed studies containing important safety information; the manufacturer is asked to include any new signals or important findings from any studies involving patients, as well as from newly completed animal toxicology studies: the format requires that all studies reviewed be listed and any signals mentioned. A separate focus of attention is any targeted new safety studies, which should be described as they are initiated, in addition to describing the results when they are first analysed.
- The *overall safety evaluation* is the most important part of the CIOMS II update. In a short report (i.e., no more than 8 to 10 pages) the manufacturer is asked to not only describe any specific safety issues relating to the drug, but specifically address any increased frequency of known toxicity, drug interactions, overdose and its treatment, drug abuse, positive and negative experience during pregnancy or lactation, effect of long-term treatment, and any specific safety issues relating to the treatment of specific patients groups, such as the elderly or the very young. The "bottom line" is whether the interim safety data remain in line with the cumulative experience to date and the manufacturer's core prescribing information.
- The final part of the CIOMS II Periodic Safety Update is any *important information received after the "data lock point"* (i.e., the time when the tables were generated from the data-bases for inclusion in the CIOMS II Safety Update). The CIOMS II report specifies the data lock-point and it should be no more than 45 calendar days before the completion and submission of the safety update.

CIOMS II reports are interval reports (i.e., non-cumulative) and they are required or submitted six months from a drug's International Birth Date (which is the date on which the first regulatory authority approved a particular drug for marketing). The idea was that the manufacturer's data are temporarily frozen for review for that particular drug every six months subsequent to the International Birth Date and that all regulatory authorities that wish to have safety updates accept the same cut-off date and time of submission.

A retrospective look at CIOMS II reports

People would no doubt agree that the CIOMS II Periodic Safety Update is not an easy undertaking for any manufacturer, for it is usually difficult to collect together all the different pieces of information from the different departments within the organization. Once written, they are very user-friendly and informative to people within the corporation as well as to those regulatory authorities that require them.

The UK and the Swedish regulatory authorities have been the most forthcoming in requesting written safety updates in CIOMS-II format.

It is interesting to see that the periodic updates which the European Union regulations require are to be submitted in the CIOMS-II format. Meanwhile, in the US, the CIOMS II format seems to be gaining increasing acceptability, although we all hope that the FDA will agree to substitute CIOMS-II reports for other current requirements, rather than asking for CIOMS-II updates in addition to their other periodic reporting needs!

The CIOMS III Working Group — Core data sheets

The first and second CIOMS working groups had to refer to a core data sheet. Whereas most companies had some sort of core data sheet for each drug, there was no consistency among manufacturers on how these should be formatted, and there are also wide differences between the Layout of the Summary of Product Characteristics as defined in Europe and in the U.S. Package Insert.

CIOMS Working Group III is considering why there should be a standard format and specifying, as far as feasible, what should be included, both in the initial core data sheets (at the time of product licence for marketing application) and subsequently as post-marketing information on the safety of a product becomes available. The group is also addressing ideas of when and where the information should be included, and other ideas which describe how best to put the information into the core data sheet, i.e. general ideas concerning good working practices. As would be expected, the third CIOMS Working Group is concerned only with safety aspects of the core data sheet.

CIOMS III home-work

As part of the exercise, each regulator and manufacturer representative in the working group produced two borderline scenarios in which it was debatable whether the data sheet should be amended. Each scenario was then evaluated by each member of the working group, who was asked to comment on his or her decision about changing the data sheet, any problems concerning "what", "when" and "where", and the wording suggested.

The working group is at present producing an early draft of its conclusions, looking at factors affecting the weight of the evidence (i.e., the threshold above which it should be decided that the drug does cause an adverse reaction), considerations about the sufficiency or importance of the information, and aspects of good practice.

Summary

Figure 2 (Annex) represents the core data sheet, and shows how safety statements can vary between countries A, B and C, whilst there is a central core. This could be the logo of the three CIOMS working

groups. The first group related expedited case reports and labelling to the core. The second gave periodic safety updates and comments on the adequacy of what is included in the core data sheet. The third is dealing with the content of the core data sheet.

What of a fourth CIOMS working group? It could be that such a group would revisit the conclusions of the first three working groups, once the regulations in Europe are clear. However, it could work on specifying in more detail the information items which are considered important for sending information from source to WHO through the intermediate data-base. You may have some other specific ideas, in which case we should be glad to hear from you.

Table 1. Information required by the regulatory authorities of the Federal Republic of Germany[a]. the United Kingdom[b] and United States of America[c] (1986)

a) Required by all three regulatory authorities:

- Patient identification, sex, weight
- Observed unwanted effect, date of onset, outcome
- Identification of suspected drug
- Drugs given, mode and dates of administration, indication
- Name of reporting doctor, address, date of report

b) Required by only one or two of the three regulatory authorities:

Date of birth (BGA, CSM)
Age (FDA)
Race (BGA, FDA)
Height (BGA, FDA)
Occupation (BGA)
Parity (FDA)
Month of pregnancy (BGA)
Week of pregnancy (FDA)
Duration of effect (BGA)
Laboratory tests (FDA)
Drug brand name (CSM, FDA)
Dosage form (BGA)
Duration of treatment (FDA)
Prior exposure to suspected drug (BGA, FDA)
Previous tolerance (BGA)
Re-challenge (BGS, FDA)
Past medical history (BGA, FDA)
History of allergy (BGA, FDA)
Smoking/drinking habits (BGA)
Progress and treatment of observed unwanted effect (BGA)
Cause of death (BGA, FDA)
Date of death (FDA)
Assessment of causality (BGA only, but required from three sources)
Information about who has been informed (BGA)
Whether information may be released (FDA)
Speciality of reporting doctor (BGA)
Signature (BGA, CSM)

[a] Bundesgesundheitsamt (BGA) (Federal Health Agency)
[b] Committee on the Safety of Medicines (CSM)
[c] Food and Drug Adminstration (FDA)

Table 2. Requirements for Periodic Safety Updates (Countries represented in CIOMS Working Group II)

Country	Before submission of marketing application dossier	After submission before approval	While drug marketed (Time post-launch, in years)	Formal post-marketing surveillance requirements
Canada	N	N	N	N
Denmark	N	N	N	N
France	N	N	0.5, 1.0, Yearly	M, Local
Germany	N	N	2, 5; then every 5 years	N
Italy	N	N	January & July every year	N
New Zealand	N	Y*	N	Y**
Sweden	N	N	N	N
United Kingdom	M	N	N	Y, "Voluntary"
United States	Y	Y	0.25 for 3 years; then yearly	M

Y = Yes; N = No; M = Maybe
* Often but not always requested by the Department of Health
** Only as requirement for reimbursement status approval

Table 3. Requirements for Periodic Safety Update Reports (Countries not represented in CIOMS Working Group II)

Country	Before submission of marketing application	After submission, before approval	While drug marketed (Time post-launch, in years)
Australia	N	N	Yearly for 3 years
Japan	N	N	Yearly; special 6 year report
Korea, Republic of	N	N	Yearly for 3 years
Netherlands	N	N	0.5 for 5 years then every 5 years
Philippines	N	Y	Yearly
Switzerland	N	N	0.5, 1.0*
Taiwan	N	N	0.5 for 3 years
Thailand	N	N	0.2 for 2 years
Proposed EC 1993)	N	N	0.5 for 2; yearly for 3, then every 5, years

Y = Yes; N = No
* Only for drugs approved under "monitored release"

Figure 1. The CIOMS form

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT	

I. REACTION INFORMATION

1. PATIENT INITIALS (first, last)	1a. COUNTRY	2. DATE OF BIRTH Day	Month	Year	2a. AGE Years	3. SEX	4-6 REACTION ONSET Day	Month	Year	8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
										☐ PATIENT DIED ☐ INVOLVED OR PROLONGED INPATIENT HOSPITALISATION ☐ INVOLVED PERSISTENCE OR SIGNIFICANT DISABILITY OR INCAPACITY ☐ LIFE THREATENING
7 + 13 DESCRIBE REACTION(S) (including relevant tests/lab data)										

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)		20 DID REACTION ABATE AFTER STOPPING DRUG? ☐ YES ☐ NO ☐ NA
15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION	21. DID REACTION REAPPEAR AFTER REINTRODUCTION? ☐ YES ☐ NO ☐ NA
17. INDICATION(S) FOR USE		
18. THERAPY DATES (from/to)	19. THERAPY DURATION	

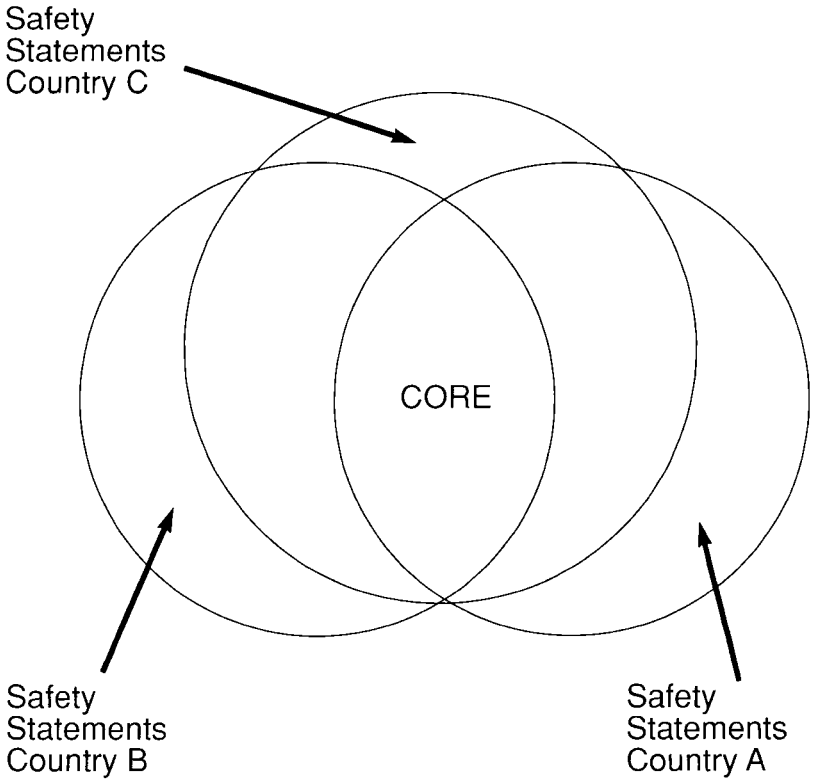
III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER	
	24b. MFR CONTROL NO.
24c. DATE RECEIVED BY MANUFACTURER	24d. REPORT SOURCE ☐ STUDY ☐ LITERATURE ☐ HEALTH PROFESSIONAL
DATE OF THIS REPORT	25a. REPORT TYPE ☐ INITIAL ☐ FOLLOWUP

Figure 2. The Core Data Sheet

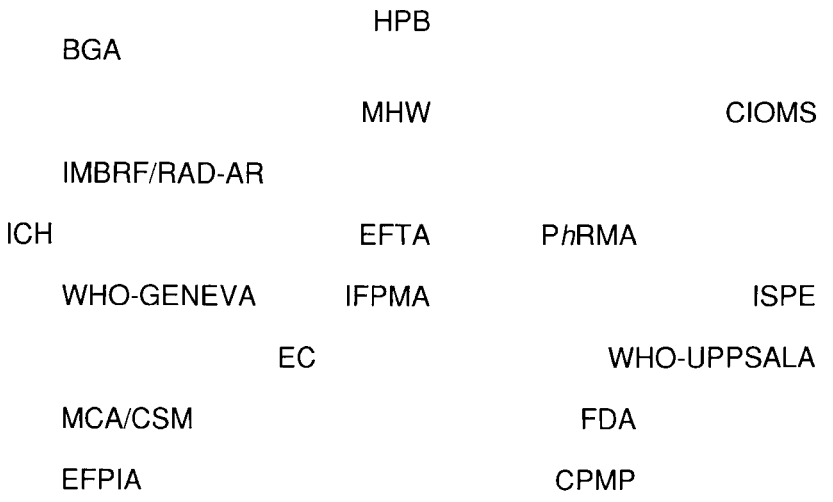


THE INTERNATIONAL CONFERENCE ON HARMONIZATION: EXPEDITED REPORTING OF ADVERSE DRUG REACTIONS

Arnold J. Gordon*

Before addressing the specific subject of my comments, I would like to share with you a situation (Fig. 1) that represents some of the frustration that many, if not all of us, experience in the field of drug safety: just who is responsible for what; who has the authority to issue guidelines or regulations or create definitions; who is important; who speaks to whom?

Figure 1. *JUST WHO*: is responsible for what? has authority? is important? speaks to whom?



This is an embodiment of the communication issues that previous speakers have raised. We all seem to be submerged in an alphabet soup of organizations, most of which you will recognize immediately. The CIOMS Group, which of course, is not an "official" group, as Dr Castle has indicated, has generated useful proposals, which have created important precedents for standardization of adverse-reaction reporting and monitoring for marketed drugs. Another significant "unifier" is, of course, the International Conference on Harmonization (ICH), which began several years ago. The regulatory authorities in the three geographic areas of the United States of America, the European

* Worldwide Harmonization, Pfizer Inc., New York, NY

Community and Japan agreed to attempt a harmonization of the technical requirements for drug development and registration (pre-marketing activities). Observers are the EFTA countries, Canada and WHO. The ICH secretariat is the International Federation of Pharmaceutical Manufacturers Association (IFPMA). The three technical branches of ICH are preclinical safety (toxicology, etc.) formulation quality issues (stability testing, excipients, etc.), and clinical efficacy and safety. Major ICH gatherings are held every two years to present accomplishments to, and obtain feedback from, a wide audience of affected parties.

Standardization of clinical-safety data

I have had the privilege of coordinating one of the ICH2 efficacy topics, referred to officially as Topic E2, "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting," which I will describe in some detail. As with each ICH topic, the expert working group (EWG) consists of a regulatory and an industry representative from each geographic region, plus an observer, if appropriate.

There is an important need for standardization in this area, which, after all, deals with key clinical safety information on a new medicine. The WHO Collaborating Centre (Uppsala) is now receiving some 100,000 reports annually from its member agencies, of which 20% are deemed "critical". The US FDA alone processes more than 80,000 adverse event reports on US marketed drugs per year, 20% on an expedited basis (15-day); about 30% of the latter are fatalities. Many factors can influence the need for rapid reporting on important safety issues. For example, is the event "serious" or non-serious; is it unexpected (not previously documented) or expected (labelled or previously reported); is it a local case or a foreign case; does the case come from a clinical trial or from another source? Unfortunately, the definitions of terms and the requirements for reporting are different in most of the 20 or so countries that do have such regulations, including how quickly to report and how to report — some countries require special local forms, some will accept a CIOMS form, and in many cases no forms are required (Fig .2).

Fig. 2. Current multiplicity of definitions and requirements for expedited reporting on drugs in development

Regulations/Guidelines:	About 20 countries
Factors governing *what* to report:	Serious vs. Non-Serious Unexpected vs. Expected Related vs. Not related Domestic vs. Foreign Clinical trial vs. Other source
When to report:	Immediately, promptly, 72 hours; 3, 10, 15, or 30 days; without delay.
How to report:	Local form, CIOMS form, no form.

Although the pre-marketing environment differs in special respects from the marketing environment, one of the important issues we had to face was the following: at least over the lifetime of those of us in this room, it is safe to say that most drugs will be approved at different times in different parts of the world, so that while a drug is under development in some countries it may very well be on the market elsewhere. So it would be ill-advised and possibly dangerous to consider only the pre-marketing environment when trying to establish regulations or guidelines for safety reporting, because the information that is collected on marketing experience surely will be of direct interest to those regulators in countries where the drug is in development or under market-application review. Therefore, the two stages should not be separated from the point of view of important safety-reporting. This is a slight departure from the ICH mandate, which is directly concerned with technical requirements during the developmental stage of a product.

Proposal for standardization of expedited reporting

As we have been hearing from other speakers, to make sure that everyone is receiving the same kinds of information in the same way, we do need agreed definitions and standards. Under E2 we chose to limit requirements for expedited reporting to those reports that are of "serious, unlabelled, adverse reactions"; each term in the quotes has been carefully defined. The proposal by our EWG has reached Step 4 (June 1994) in the ICH process (sign-off by all three regulators). It was officially released as a Step-2 paper in June 1993 for critical review and comments; the Step-4 version emerged following the October 1993 ICH-2 Conference (Orlando, Florida).

In developing the proposal we drew heavily on definitions already developed by WHO for application to marketed products. An adverse

event refers to any occurrence of an adverse finding whether or not drug-related; "reaction" refers to the fact that there is thought to be a causal relationship between drug and event. We also had to distinguish between the terms "serious" and "severe"; the former is a medical/administrative determinant for reporting, the latter a relative intensity (as in mild, moderate, or severe headache). The definition of "serious" is very similar to, but not identical with, the definitions now in place in other parts of the world, such as under CIOMS I for marketed drugs, under FDA regulations, and under other regulatory bodies.

"A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. *These should also usually be considered serious.*"

Regulator and industry parties in ICH have, I believe, captured the meaning and the spirit of all of them. Note the expression in the first sentence, "at any dose"; it was inserted specifically to cover the use of a drug in overdose. When a drug is under development and not on the market anywhere in the world, manufacturers are expected to have a standard Investigators' Brochure, which will be the same everywhere the drug is studied; the Investigators' Brochure, when appropriately constructed and updated, will contain all important safety information and will serve as the relevant source document for expectedness.

The primary reports are of single cases of serious, unexpected adverse drug reactions. As under CIOMS I rules for marketed drugs, it was decided that a spontaneous report would have implied causality. In a clinical-trial case, one usually has access to much more detailed information and is required to perform a causality assessment. If either the reporting physician or the sponsor believes the drug is causally related, expedited reporting is required. In general, it is not important to report in an expedited fashion anything except serious, unexpected, adverse drug reactions (ADRs); expedited reporting of all other categories have the effect of diluting the attention needed for those very important cases, particularly for a drug still under development. Other criteria also have been established for expedited reporting. For example, new cases with greater severity or more specific pathophy-

siology would be "unexpected" (fulminant hepatitis vs. hepatitis). A clinically significant increase (without strict definition of this phrase) in the rate of occurrence of an "expected" (known) serious ADR is also reportable. Other observations involving medical and scientific judgment on reporting include a significant hazard to a study population, such as lack of efficacy of a drug used to treat a life-threatening condition, or a major safety finding from an animal study (carcinogenicity, for example).

Reporting to regulators

How should the information be submitted to regulators? It is suggested but not required by the proposal that the CIOMS form be used as a simple, standard summary to capture the basic facts on the case; but primarily, the key is the inclusion of basic data elements on each case (the subject, incidentally, of a new CIOMS initiative known as CIOMS-IA). The basic data elements are: *patient details, suspected product, other treatments, details of suspected ADRs, details on reporter of events, and administrative/sponsor details.* However, a company should feel obligated to report a case even if all the details are not available, as long as four minimum criteria are satisfied; these criteria are: *an identifiable patient, a suspect medicinal product, an identifiable reporting source, and an event or outcome identifiable as serious and unexpected, and for which in clinical investigation cases there is a reasonable suspected causal relationship.* Thus, regulators are made aware initially of a potential serious ADR, with details to follow in subsequent reports.

Agreement was also reached on the timing for reporting to all appropriate health authorities relative to the first time anyone within a company has sufficient knowledge that a case qualifies:

Fatal and life-threatening reactions — 7 calendar days
All other serious ADRs — 15 days.

For the rapid alert, 7-day reports, follow-up with as much detail as possible is required within eight additional calendar days. With regard to the situation involving a blinded-study report, the EWG proposal advised that the code should be broken for an individual case that qualifies for reporting. This is not expected to compromise the integrity of the study and it facilitates better understanding and communication of risks, especially when the Investigators' Brochure and informed consent are involved.

Further harmonization tasks

It is expected that the E2 proposal will be implemented at the regulatory level within all three ICH regions during 1995. However, harmonization of many other aspects of safety reporting is needed. Examples include the reconciliation of differences that still remain between certain definitions and reporting standards for pre-marketing

and marketing phases; development of international standards and specifications for paper and electronic reporting and exchange of individual AE/ADR cases; and consideration of the nature and amount of information for periodic, summary reporting that should be gathered and assessed on a medicine while under development. It is hoped that these and other issues will be addressed as topics under ICH3.

[*Note:* This paper is an updated version of the author's presentation at the Conference]

STANDARDIZATION OF ADVERSE EXPERIENCE TERMINOLOGY

Raymond Herman*

As President of the COSTART Users Group in the United States, and having been involved in drug safety in the pharmaceutical industry for the past 14 years, I should like to share my views with you regarding the standardization of adverse-experience terminology. COSTART is the official post-marketing adverse-experience dictionary of the US Food and Drug Administration, and more than 70 pharmaceutical companies in the US use COSTART in its pure or a modified form. These companies are members of the Users Group, whose main functions are to educate the user for COSTART use and to liaise with FDA on areas of concern with the dictionary.

Needless to say, there are concerns with COSTART, just as there are with WHOART, as both dictionaries were heavily derived from a dictionary called DART, which was in place for both the World Health Organization and the FDA in the mid-1960s. Besides the common complaint that some therapeutic areas (e.g. infectious diseases) have been given little coverage, as well as placements that could be more medically correct, the concern of late is why we need two major different dictionaries or thesauri, when so much attention has been given to international standardization efforts. I refer, of course to the initiatives of WHO, CIOMS, the International Conference on Harmonization (ICH) and other bodies.

A COSTART or WHOART dictionary is, in effect, a thesaurus of adverse-experience terms. And these terms are the result of a distillation of natural language into a workable subset for simple data-base retrieval and analysis. This process is known as vocabulary control. One must be very cautious of any vocabulary control system as it provides only a rapid and partially accurate picture of the actual events reported. Hence we must constantly remain suspect of the thesaurus and not ascribe to it more credibility than it deserves. The authors of the 1970 COSTART manual stated in the preface: "it cannot be emphasized too strongly that COSTART is not designed to be an end in itself. Its entire construction is predicated upon the capability to provide selective, consistent and inclusive retrieval of data entered into the computer". While we must be prepared to lose a degree of specificity when employing COSTART, we must also remember the reasons for this loss. The results allow a consistency, albeit a loss of specificity, to achieve a simplified safety-profile with the ability to raise questions or concerns. It is the consistency aspect of an adverse-drug-experience vocabulary control system which begs for international standardization.

* ICI Americas, Pharmaceuticals Group, Wilmington, Delaware, USA

What must we do, and, if we do it, what will be the final result?

First, the proprietors of the major dictionaries need to accept the concept of universal standardization. Professor Edwards has been pursuing this for a few years now, so the idea has been well disseminated to members of WHO. On the other side of the Atlantic, I, representing the COSTART Users Group, as well as Professor Edwards, have met with the FDA and spelled out what it is we should like to accomplish. Those proposals have received general acceptance along with a promise of active participation in the near future.

This commitment by the FDA implies that in the US a concurrence needs to happen within the FDA for submission of reviews of adverse experiences in both the pre- and the post-marketing areas. The concurrence means that all FDA reviewers will accept and use the same agreed-upon thesaurus.

Action of this type would be a major impetus to the standardization effort and would certainly be welcomed by pharmaceutical manufacturers, who constantly have to modify terminology to suit the regulatory registration reviewers' own preferences. Of course, for this project to be fully successful, it would be not only advantageous but also advisable to have the acceptance of the other regulatory reviewing agencies of major adverse-experience reporting countries.

Another area that requires consideration for this project to succeed is definitions of terms — the words behind the words. Are we using adverse-experience terminology in the same way? Does "the event which is reported" mean the same thing, medically and universally? Those of us who work in the drug safety areas, internationally, know the answer already. And that answer is "not in all cases". Once one crosses country borders, it is not unusual to find differences in medical definitions. And this will occur even though the spoken language is the same! Even yesterday, we heard Dr Rawlins tell us to ignore the data on leukopenia in the UK/US study because the definitions of the adverse experience were different.

The consensus definitions that have been put forth by CIOMS and Dr Bénichou have been pivotal for medical science but, as we are aware, an iron-clad diagnosis requires considerable information for precision. Regrettably, we usually do not obtain that degree of information in the conduct of clinical trials or in the body of spontaneous reports received after a drug has been marketed. However, this is not to say that definitions of adverse-experience terms are unnecessary. On the contrary, we need to look towards clinically descriptive definitions that can be useful for even the anecdotal data we receive in post-marketing reports, if we are to have international acceptance of a standardized terminology.

The COSTART Users' Group has previously presented what we believe constitutes the ideal system and what we should work towards. I should like to share these ideas and goals with you:

1. The system should embrace the concept of one world-wide thesaurus.
2. It should have world-wide regulatory acceptance.
3. It should contain clinically descriptive terminology.
4. It should have appropriate categories and terminology so that:
   - one can derive easy labelling-information
   - a safety profile can be clearly presented
   - it is appropriate for international pharmacovigilance — it is appropriate for pre- and post-marketing use
   - it can avoid the deficiencies in the current terminology.
5. It should be developed with the assistance of medical and coding experts.
6. It should provide authorized translations in major languages.

If we can help to achieve these objectives, drug safety, as we know it, will become considerably more understandable.

SESSION IV

CHALLENGES FOR DRUG SURVEILLANCE

Chairman: John H. Bryant

Educational Aspects

Needs in Developing Countries

Management of:

- ***malaria***
- ***onchocerciasis***
- ***tuberculosis***

Monitoring the Safety of Biological Products

DRUG SURVEILLANCE AND EDUCATIONAL CHALLENGES

Molly Thomas*

Early tragedies of drug use have taught us the need to monitor drug safety, efficacy and quality. The ease with which drugs can today reach any part of the world makes this all the more important.

Problems of drug surveillance in India and other developing countries

Various post-marketing surveillance techniques have been used and much has been published on this. The spontaneous monitoring of adverse drug reactions, widely popularized in the United Kingdom and Sweden and in many other Western countries, has yielded sustained interest and has aided in many pharmaco-epidemiological pursuits. However, the developing countries have not kept pace with those countries mainly because of lack of recognition, evaluation and notification of ADRs. In many developing countries, indigenous systems of medicine have a major role and self-medication with them is very common. The composition of these indigenous products is obscure and many contain allopathic drugs as well. Hence if reactions occur, it is difficult to identify the possible causative ingredient. As access to over-the-counter drugs is unlimited and there are no means of monitoring prescriptions, drug reactions cannot be easily traced to a particular drug. Many drug reactions simulate clinical conditions. The severity of illness in a grossly malnourished population makes recognition of a reaction all the more difficult. Patients flit from doctor to doctor and pharmacy to pharmacy, thus adding to the confusion.

Physicians are not sure whether it would be to their advantage to report reactions. Fear of enquiries and misguided notions that drug reactions are evidence of therapeutic inadequacy prevent them from reporting.

There is no organized continuing medical education and often the only updates come from pharmaceutical representatives. Experience from the West has shown that the success of drug surveillance depends particularly on education and awareness among doctors, consumers and drug regulatory authorities.

The programme of monitoring ADRs is limited and it is only recently that, in addition to industry-directed surveillance, voluntary reporting has been encouraged by private or voluntary and governmental agencies.

* Department of Pharmacology & Clinical Pharmacology & ADR Monitoring Centre, Christian Medical College Hospital, Vellore 632 004, India.

Conventional educational benefits of post-marketing surveillance

The traditional value of post-marketing surveillance in generating or testing hypotheses and quantifying hazards of drug treatment in the outpatient setting is well known. Results have been used to look for associations between drugs and disease, such as aspirin and gastrointestinal bleeding, or coffee and non-fatal myocardial infarction.

ADRs can be used to identify hazards, establish causality and estimate incidence. The estimation of incidence may be a difficult task as the drug-use denominator is not readily ascertained.

Risk/benefit judgment of new classes or groups of drugs introduced can be made from ADR data. However, for the developing countries, the greatest educational challenge of ADR monitoring is improvement of drug use in the community.

Drug surveillance can be used as a challenge to educate the parties concerned in a number of ways.

1. Awareness building

An adverse reaction is often thought of only as an inconvenience to patients and doctors. Awareness building should start early in both medical and community education. For largely illiterate populations, maximum use should be made of audiovisual and traditional forms of dissemination of information.

Medical education should give more attention to ADR recognition and evaluation as well as to communication skills. Too little time is spent with patients and in explaining drug use to patients, and means of communicating with "illiterate" patients are neglected.

The importance of taking a drug history and looking for drug reactions must be stressed. Most undergraduate teaching does not stress adverse reactions to drugs in terms of drug safety, efficacy or risk/benefit.

Simple visual reinforcement by means of videos that depict typical drug reactions can be used to enhance education. The stress should be on selection of drugs for a disease from the large range of drugs available. Scoring techniques to assess selection of drugs in which safety and efficacy are included are useful. Problem-solving exercises can be worked around ADRs to emphasize drug safety.

2. The cooperation and education of physicians

Primary care physicians are the backbone of health care in any country. To enable them to participate in post-marketing surveillance, early exposure and follow-up are needed. Good rapport with the physician and the use of simple ADR-reporting forms could give a reasonable response. The use of practitioners' own reports as educational tools could also improve reporting.

i. Through easily read **newsletters** or other forms of feedback issued periodically, practitioners can be notified about the ADRs being reported. An acknowledgement by name in the newsletter of doctors who respond might motivate them to report more frequently.

ii. Analysis of ADR reports can reveal doctors' **prescribing patterns**. It is most difficult to get this information direct from physicians but, if it can be gathered in a non-threatening way from the reports, the offending drugs and the conditions for which they are used can be revealed. Some reported reactions have been caused by drugs of which the efficacy and safety have been questioned elsewhere. A newsletter can use such information to illustrate the need to avoid selecting a potentially dangerous drug when safer alternatives are available; also it can highlight drug interactions.

Many irrationalities of drug use can be gathered from ADR reports and these can be used to promote rational drug use. The newsletter and feedback should open up easy communication channels between the doctors and the reporting centre.

iii. **Containing the cost of treatment**. Mostly patients pay for their treatment. ADR reports can be correlated with length of treatment or hospital stay to assess the economic burden that ADRs impose upon the patient and the community. This can be very significant for poorer countries with meagre health-care resources and no health insurance coverage.

iv. **Curbing the inappropriate use of antibiotics**. A major problem in developing countries is the indiscriminate use of antibiotics. ADR reports can indicate prescribing patterns and trends in using antibiotics for viral fever, diarrhoeal diseases etc., and these can be brought to the notice of physicians.

New antibiotics still untried in tertiary-care hospitals are very often freely available in the community; for example, four years ago when ciprofloxacin was used only in selected cases of enteric fever, it was the most commonly used drug for fever in urban general practice; not only was its use an unnecessary expense, but its indiscriminate use resulted in multi-drug-resistant *salmonella typhi*.

There has been similar inappropriate use of mega-dose vitamins, tonics and injections. Once such problems are identified, doctors may be educated by such means as workshops and lectures, through medical associations or other agencies. Workshops have the advantage of bringing people together and are an educationally ideal means of introducing and updating concepts in therapeutics and the rational use of drugs and improving clinical competence. It is essential to establish good rapport and give primary support with drug information. The participation of general practitioners gives them a sense of involvement and accountability, and boosts their morale and self-esteem.

3. Training of pharmacists

In most developing countries, pharmacists are the first point of contact for patients and hence play a pivotal role. Since transactions cover diagnosis, prescribing and advising on the effective use of a prescribed medicine or self-medication, and over-the-counter drugs are expected, pharmacists should be trained in the necessary expert knowledge and skills. Pharmacists are the first health professionals likely to receive reports from patients about possible reactions to medicaments purchased with or without prescription. Hence, primary-care pharmacists can do much to ensure that maximum information on possible ADRs is made available to central reporting centres and in educating the public.

Printed information or a training manual on drug use, with emphasis on post-marketing surveillance, would be useful, as well as workshops for physicians and pharmacists.

4. Educating the community

The community at large is ill-informed about drugs and their uses or side-effects. Where self-medication is common and many drugs can be bought over the counter, communities should be educated about drug use. They should be taught to recognize early reactions and report them to the nearest physician if possible. Since levels of literacy may be low, visual communication media such as videos and television shows in community halls are likely to be more useful than print media. "Street drama" performances depicting drug-related events can be enacted to retain interest and educate. In view of the growth of consumer protection associations and of awareness of individual rights, information about ADRs should be disseminated impartially. Early teaching about drug use and the hazards of medication could be encouraged in schools.

5. Manufacturers

Manufacturers should stress quality assurance and update drug datasheets. Adverse reactions to a drug should be the same in developing and developed countries, except where genetic differences occur. Industry is very influential and can reach practitioners in remote areas. It is very important that medical representatives be trained to give rational promotional material. Industry can do much to improve drug use and can be a good resource for notifying drug reactions and for education.

6. Health authorities and regulatory agencies

Health authorities can use information on ADRs in ascertaining risk/benefit ratio and safety assessment of drugs. Epidemiological profiles

that can be constructed from ADR reports could be used to introduce drugs cautiously among vulnerable populations, and could help also in checking for quality assurance and spurious drugs.

7. The mass media

The education of this group is of paramount importance, as irresponsible reporting can do much harm. There should be a mechanism for informing them responsibly so that they give wide publicity when necessary to educate doctors, patients and the community.

In conclusion, the crucial challenge of education from drug surveillance lies in ensuring its relevance to community health, promoting the principles of rational prescribing, and cultivating a discerning attitude towards cost of treatment.

NEEDS IN DEVELOPING COUNTRIES: CURRENT STATE OF ANTIMALARIAL DRUG RESISTANCE

Nicholas J. White*

Introduction

Although malaria is estimated to infect about 5% of the world's population at any time, and to kill between one and two million children a year, there are remarkably few drugs available for its prevention and treatment. Research during the Second World War and the conflict in Viet Nam brought us most of the drugs we have today. The list is short, and the development of new compounds has not kept up with the parasite. *Plasmodium falciparum* has developed resistance to all of our available drugs, and *Plasmodium vivax* has developed resistance to chloroquine in some parts of New Guinea. Multi-drug resistance in *P. falciparum* is particularly serious in South-East Asia, and the possibility of completely untreatable malaria in the near future must be considered seriously.

All antimalarial treatment regimens are associated with some failures (Bruce-Chwatt, 1981). In the last three centuries, the bark of the cinchona tree was the only specific remedy available for the treatment of malaria in the Americas and Europe. Laveran's discovery of the malaria parasite in 1880, and his subsequent demonstration that quinine killed these intra-erythrocytic organisms, finally characterized the specific antimalarial action of the alkaloid content of cinchona bark.

Research stimulated by the two world wars led to the introduction of mepacrine (quinacrine) and chloroquine, and the discovery of the antimalarial biguanides proguanil (chloroguanide), chlorproguanil and, somewhat later, amodiaquine and pyrimethamine (Covell et al., 1955; Coatney, 1963); it also laid the foundations for the development of other antimalarial quinolines and acridines, and also the hydroxynaphthaquinone compounds. There have been only a few more recent additions.

Between 1963 and 1976 the US Army screened over 250,000 potential antimalarial compounds, which led to the discovery and development of mefloquine and halofantrine. The first reports in 1961 of chloroquine resistance in *P. falciparum,* in both South America and South-East Asia, were further incentives to research. By then chloroquine had become the standard antimalarial for treatment and prophylaxis of all the human malarias and, as a consequence, one of the most widely-used drugs in the world. At first, resistance to chloroquine was low-grade and geographically focal, but during the ensuing years

* Faculty of Tropical Medicine, Mahidol University, Bangkok 10400, Thailand; and Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, UK.

treatment failures increased in number and degree. By the beginning of the 1980s, chloroquine was no longer effective for the prevention or treatment of falciparum malaria in many parts of South-East Asia and South America, and the ominous first reports of chloroquine resistance were emerging from the east coast of Africa. Over the past ten years, resistance has spread inexorably from the east to the west coast of Africa. Most countries in the tropics are now affected (World Health Organization, 1990a). Only central America (North of the Panama canal) and North Africa are still free.

The development of antimalarial drug resistance

How do malaria parasites develop resistance to the antimalarial drugs? The selective pressure exerted by drugs takes place during asexual multiplication in the human host. The sexual forms (gametocytes) of *P. falciparum* but not the other malaria parasites of man are relatively resistant to the antimalarial drugs (with the exception of primaquine). Parasite meiosis takes place following random mating between the sexual forms in the gut of the female anopheline mosquito. After sporogony (the development of sporozoites) in the mosquito, the genetically-mixed variants are then redistributed to humans at subsequent feeding. Naturally-occurring populations of *P. falciparum* are genetically diverse, with heterogenous sensitivity to the antimalarial drugs (Thaithong, 1983). Infections are usually polyclonal. Resistance probably results from spontaneous chromosomal point mutations (this is thought to be independent of drug pressure), followed by selection of the more resistant mutants under antimalarial drug pressure. Although resistance to the dihydrofolate reductase (DHFRT) inhibitors (pyrimethamine, proguanil) can arise from single or two-point mutations, epidemiological and laboratory observations suggest that resistance to the quinoline compounds is likely to require a series of unlinked additive mutations. Significant resistance to the artemisinin derivatives has not been confirmed yet. Models of the development of drug resistance have been developed (Curtis & Otoo, 1986; Cross & Singer, 1991) and have some important practical implications. These models predict that resistance will develop rapidly if maximally effective antimalarial treatment is given to more than 25% of the population in areas of intense transmission (e.g. sub Saharan Africa, New Guinea). In theory, the use of antimalarial combinations delays the onset of resistance, but only if the parasite resistance genes are rare and free recombination can occur between them, and if less than 20-25% of the population is treated (Curtis & Otoo, 1986).

Selection of the resistant parasites is most likely if the heterogenous parasite population is exposed to a sub-therapeutic level of drug. For resistance to spread, the selected more resistant parasites must then survive to produce gametocytes, and these parasites must be transmitted. There should not be a major survival disadvantage for

these resistant parasites. Anopheline mosquitoes differ in their receptivity to different parasite strains; in some circumstances the principal vectors are more receptive, and in others less receptive, to resistant parasites (Wernsdorfer, 1991).

In practice, antimalarial drug resistance is likely to develop in three sets of circumstances: (a) widespread and extensive antimalarial drug use; (b) generally inadequate dosing (doses too low, or more usually treatment courses that are too short); and (c) adequate dosing with drugs that are eliminated slowly from the body. Inadequate dosing occurs commonly because of poor compliance with prescribed antimalarial treatment regimens, or unregulated antimalarial drug distribution and self-prescribing. Both are common. The greatest pressure occurs when the whole population has low antimalarial drug concentrations constantly in the blood.

There has been considerable progress in recent years in characterising the mechanism of antimalarial drug resistance. The precise molecular basis for resistance to the dihydrofolate reductase inhibitors has been identified to single or double base pair mutations. The gene or genes responsible for chloroquine resistance have been localised to a 4 000 base segment of the parasite's chromosome 7 (but not as yet characterised). The importance of the multiple drug resistance (mdr) genes and their products which pump drugs out of cells has been a subject of considerable interest and debate but their overall contribution to drug resistance is not yet resolved. Many important practical questions need to be addressed. For example, would it be possible to preserve or regain chloroquine efficacy? Perhaps drug sensitivity would return if chloroquine were no longer used, thereby removing the selective pressure on resistance? This has been suggested but never proved. Indeed most data suggest that the chloroquine-resistant phenotype is stable. In practice it is very difficult to restrict use of chloroquine, particularly as it remains the antimalarial drug of choice for the other three human malarias. Cross-resistance between antimalarial drugs of the same group is another potential source of drug pressure, but one which has not been quantified adequately. For example, could use of the 4-aminoquinoline amadiaquine drive chloroquine resistance? Does widespread use of co-trimoxazole for treating bacterial infections encourage resistance to antimalarial antifolates? Does use of mefloquine drive quinine resistance? We do not have answers to these questions.

Chloroquine resistance

In the past, there has been a tendency to declare falciparum malaria in a country 'chloroquine-resistant' if returned (non-immune) travellers with the infection fail after chloroquine treatment or if *in vitro* sensitivity tests indicate resistance. These reports do not assess the usefulness of the drug in the indigenous population, which usually has

some immunity, and in which the drug may still retain efficacy. Even though nearly all countries in sub-Saharan Africa now have evidence of chloroquine-resistant *P. falciparum*, chloroquine remains the most widely-used antimalarial on the continent, and is still a most valuable drug. In Africa, transmission is usually intense and, as a consequence, malaria is largely a problem of childhood. In 1988, 91 metric tons of chloroquine were consumed (World Health Organization, 1990a), corresponding to approximately 500 million child-treatment doses. Chloroquine can be purchased readily without prescription, and is used as a cure-all for fevers and a variety of minor ailments. It has an extremely long (c. 1-2 months) terminal elimination half-life (White, 1985). In many places the majority of the population has detectable blood concentrations of chloroquine at any time. This is the 'drug-pressure' that drives resistance. Where transmission of malaria is intense, reinfection occurs rapidly after treatment and the newly acquired parasites are exposed to low blood concentrations of chloroquine. If there is low-grade resistance and some background immunity, there will be a satisfactory symptomatic response to chloroquine treatment (Brandling-Bennett et al., 1988). Severe infections will respond reliably to treatment, i.e. the drug is still very useful. Unless children are followed up for several weeks after chloroquine treatment, the full adverse effects of resistance will not be appreciated. There is now clear evidence from Africa that the main adverse effect of rising chloroquine resistance in endemic areas is anaemia in childhood. This has serious consequences but can be overlooked easily if the immediate clinical and parasitological indices of response are relied upon as the sole indicators of drug efficacy. As resistance worsens in areas of high transmission, the therapeutic response slows, and increasing numbers of infants with severe anaemia are seen. Eventually the number of infections with an unsatisfactory response to treatment rises to the point where chloroquine is no longer useful, and alternative drugs are recommended. In most countries quinine has now replaced chloroquine as the treatment of choice for severe malaria (although there is some evidence that in fully sensitive infections chloroquine is the better drug). The decision when to change treatment recommendations is difficult and depends on knowledge of the local therapeutic response *in vivo*, and the cost and availability of alternative drugs. Chloroquine is still a very useful antimalarial drug in Africa; indeed in many areas, it is still the only drug available for uncomplicated malaria, but resistance will continue to increase and more and more countries will be forced to find alternatives in the near future.

After chloroquine; what next?

What are the alternatives to chloroquine? Amodiaquine is structurally similar but is more active against moderately chloroquine-resistant

strains, although the difference is not great. Prophylactic use of amodiaquine has been discontinued because of the high incidence of agranulocytosis (1 in 2000) and hepatitis (Hatton et al., 1986), and this has cast a shadow over its role in treatment. The combination of a long-acting sulphonamide (sulfadoxine, sulphalene) with pyrimethamine or antimalarial biguanide (proguanil, chloroproguanil) together with a sulphone (dapsone) are synergistic and active against *P. falciparum* in some areas where pyrimethamine alone is not. These combinations are well tolerated and have the practical advantage of single-dose therapy. Unfortunately, resistance to these drugs has developed rapidly in South-East Asia and South America, although both sulphonamide-pyrimethamine and sulphone-biguanide combinations are still very effective in East Africa (Watkins et al., 1988b) and have replaced chloroquine in some countries.

Despite over 350 years of continuous use, quinine remains an effective treatment for malaria. Quinine sensitivity in *P. falciparum* has decreased in some areas but there is still no convincing evidence of high-grade resistance, i.e. complete failure to respond in the presence of adequate blood levels (Looareesuwan et al., 1990). *In vitro* tests of antimalarial sensitivity of *P. falciparum* in Thailand, where multi-drug resistance is a particular problem, are now indicating a worrying increase in the rate at which quinine resistance is increasing (H.K. Webster, personal communication). In Thailand, the therapeutic response to quinine in severe malaria did not change significantly in the 1980s, but in the past three years there has been a significant decline in the therapeutic response (Pukrittayakamee et al., in press). Thus the cinchona alkaloids, quinine or quinidine, can still be relied upon in severe malaria (World Health Organization, 1990b), but in some areas this may change relatively soon.

Several antibacterial drugs have antimalarial activity, although most are not reliably effective when used alone. The new macrolides, particularly azithromycin, have excellent antimalarial activity *in vitro*, and will be evaluated for both prophylactic and treatment efficacy in the near future. Rifampicin also has weak antimalarial activity, and has been shown to be active against vivax malaria in man, but its value in combinations is not know.

Mefloquine is a quinoline-methanol compound active against most multi-drug-resistant strains of *P. falciparum* , although some West African strains appear to be intrinsically resistant (Simon et al., 1988). Resistance has developed rapidly over the past four years since 1989, despite strict regulation of mefloquine use (Nosten et al., 1991). There is also concern that mefloquine resistance may encourage resistance to quinine — the only drug available for the treatment of severe chloroquine-resistant malaria. Fortunately, mefloquine is still effective in most tropical countries, and those infections which recrudesce after

mefloquine treatment will usually respond to the quinine-tetracycline combination.

The immediate future

The immediate prospects are not good. There are very few new antimalarial drugs, and most countries cannot afford to buy them anyway. Halofantrine is intrinsically more active as an antimalarial than mefloquine (ter Kuile et al., 1993) and, apart from occasional diarrhoea, is generally very well tolerated in comparison with other drugs (Watkins et al., 1988a). In particular, halofantrine does not have adverse central-nervous-system effects and for this reason patients often prefer it to mefloquine. However, it has variable oral bioavailability and it is structurally similar to mefloquine. Cross-resistance is seen *in vitro* and may be a problem in clinical use (Webster et al., 1985). The standard one-day, three-dose halofantrine regimen (24 mg/kg) is effective in semi-immunes, or where parasites are highly drug-sensitive, but longer courses are required for the treatment of multi-drug-resistant malaria (ter Kuile et al., 1993).

The Chinese drugs related to ginghaosu (artemisinin) are the most important antimalarial drugs to be discovered since chloroquine. They are structurally unrelated to the other known antimalarials. Several different preparations and formulations are available for parenteral, rectal and oral administration. All have a common biologically-active metabolite, dihydroartemisinin. This is also the starting point for the synthesis of derivatives. They have proved safe and effective in China (Quinghaosu Antimalaria Coordinating Group, 1979), and over the past 15 years it has become clear that they are more rapidly acting than either quinine or chloroquine in severe malaria (World Health Organization, 1990b).

The Chinese scientists have developed other antimalarial drugs too, notably pyronaridine and nitroquine, but these have not been used outside China, and their potential role in treatment remains to be determined (Ding, 1988).

Unfortunately, despite the considerable amount of research conducted in the US Army's antimalarial drug development programme in the 1960s and 1970s, and the extensive work in China over the past 20 years, antimalarial drug development has not kept pace with resistance in the parasite. It is hoped that improvement in existing drug regimens, the cautious introduction of the new antimalarial compounds and, if necessary, a return to quinine, will buy some time, but if no more new drugs are forthcoming (which seems likely) there is a real prospect of completely untreatable malaria within the next ten years.

Which drugs?

Prophylaxis

This is a most difficult area. In many situations there are no right answers, and recommendations on antimalarial regimens are a compromise which must be under constant scrutiny and review. Where sensitive *P. vivax* or sensitive strains of *P. falciparum* only are seen, chloroquine is an appropriate prophylactic. As resistance begins, an increase in the usual weekly chloroquine dose from 5 to 10 mg base/kg (or daily administration of 1.5 mg/kg) will prove more effective, but this will be only a temporary holding measure. On what will happen afterwards opinions have diverged. The European practice has been to recommend chloroquine and proguanil for most places, in the knowledge that this combination would not be completely effective everywhere but at least would prevent severe disease and death. The combination is well tolerated and remains effective over much of Africa, southern Asia, and some parts of Oceania and the Americas. Where multi-drug resistance is more prevalent in South-East Asia, there are three options: (a) weekly mefloquine; (b) daily doxycycline; and (c) presumptive treatment with either mefloquine, halofantrine or quinine plus tetracycline. Recent evidence from two large prospective studies of the use of mefloquine prophylaxis suggests that mefloquine is reasonably well tolerated, and is more effective than other regimens in areas with resistance (Lobel et al. 1993; Steffen et al. 1993)

. Indeed the incidence of neurotoxicity in one study ($\approx$ 1:10 000) was similar to that associated with chloroquine — i.e. ten times less than with treatment. As a consequence many authorities are now recommending weekly mefloquine as a first-line choice for prophylaxis over short periods (< 3 months). In all cases, local knowledge of transmission areas and of antimalarial drug sensitivity is essential in giving the appropriate advice. Antimalarial prophylaxis is often not needed at all — for example, most tourists who visit South-East Asia do not need to take it. Even if prophylaxis is only partially effective, it will probably attenuate the development of the resistant infection, and thus reduce the risk of death (provided the patient and the physician consider the possibility of malaria in the differential diagnosis of subsequent fever). Poor compliance is a major confusing factor in all these assessments, and is an important factor contributing to 'apparent drug resistance' and malaria fatalities in returned travellers.

Treatment

Travellers returning home from the tropics with malaria are likely to have little or no immunity, and may not know the antimalarial drug sensitivity patterns of parasites in the area where they contracted malaria. In such cases, to be on the safe side, falciparum malaria should be considered resistant, if there is any doubt. In most countries in the

tropics, cost is probably the major factor in determining treatment policies and therapeutic practice locally. The other important factor is information on antimalarial drug sensitivity. *In vitro* testing of antimalarial drug sensitivity has been refined and simplified over the past ten years, and is now available to most countries with malaria problems. The information provided by *in vitro* testing is interesting for the scientist and tropical epidemiologist, but not very useful in clinical practice. It has never led to a change in treatment recommendations. What health authorities and workers need to know are the *in vivo* responses to antimalarial treatment and it is these that they act on. The sources of information on *in vivo* response vary from detailed prospective research assessment of drug efficacy in a particular community (and usually patient group) to the clinical impressions of health workers, who may notice that, more and more, patients seem to be coming back with malaria again within a few weeks of treatment. These impressions can be very insensitive; a high incidence of low-grade drug resistance (R_I) can easily go unnoticed. As there are so few antimalarial drugs available, their effectiveness needs to be monitored carefully and repeatedly, and the compliance with an adverse effects of different drug regimens evaluated.

The failure of a malaria infection to respond to antimalarial treatment results either from host factors (pharmacokinetics, compliance) which result in an insufficient concentration of the drug in blood available to the parasites or from the intrinsic resistance of the infecting parasite population to the drug treatment. All these factors can be characterized. The pharmacokinetic properties of most antimalarial drugs in a variety of patient groups have been defined in recent years because of the availability of precise (usually HPLC) drug measurement techniques. These assays are now available more widely, and antimalarial blood levels should be measured in studies investigating drug resistance.

As resistance develops, increasing numbers of late recrudescences occur. The initial therapeutic response is satisfactory, the patient recovers but the infection returns later. Patients whose parasitaemia declines slowly may be more likely to have a subsequent recrudescence; in the case of mefloquine, persistence of parasitaemia beyond day 4 following treatment in Thailand predicts subsequent failure reliably (ter Kuile et al., 1992). As resistance increases, progressively more patients are seen whose infections do not resolve (RII and RIII; high-grade resistance).

It is at this point that treatment recommendations must change if possible. Recommended antimalarial drug regimens have changed in recent years with a greater understanding of the pharmacokinetic and pharmacodynamic properties of these compounds (Winstanley & Watkins, 1992; White, 1992). There is probably some room for further improvement of current regimens, but the basic problem

confronting the tropical world is that there are not enough new drugs, and not enough research is being conducted on antimalarial drug development.

Treatment studies

Detailed guidelines for the conduct of *in vivo* clinical evaluations of chloroquine sensitivity have been published (Bruce-Chwatt, 1981). A recent World Health Organization Scientific Group (World Health Organization, 1990a) advised that 'simple and sustainable systems for the identification and reporting of antimalarial side-effects should be developed' and that the 'frequency of treatment failures should be carefully monitored and reported to health authorities', but it does not say how these recommendations could be effected. Most tropical countries have not the academic or health infrastructure to comply with these recommendations.

If *in vivo* testing stations could be set up in malarious areas, conducting simple *in vivo* studies of antimalarial drug efficacy, the results provided would give health authorities and the medical profession the information they need to decide upon appropriate antimalarial treatment. More detailed assessments of drug toxicity, blood concentration measurements, and determination of other malariametric indices could be added where necessary. The costs and benefits of newer, and nearly always more expensive, drug regimens could be gauged with certainty and the inexorable march of drug resistance defined.

References

1. Brandling-Bennett AD, Aloo AJ, Watkins WM, Boriga DA, Kariuki DM, Collins WE. Chloroquine treatment of falciparum malaria in an area of Kenya of intermediate chloroquine resistance. *Trans R Soc Trop Med Hyg* 1988; **82**: 833-847
2. Bruce-Chwatt LJ,. Ed. (1981). *Chemotherapy of Malaria,* 2nd edn (WHO Monograph Series, 27). World Health Organization, Geneva
3. Coatney GR. Pitfalls in a discovery: the chronicle of chloroquine. *Am J Trop Hyg* 1963; **12**: 121-128
4. Covell G, Coatney GR, Field JW, Singh J. *Chemotherapy of Malaria.* (WHO Monograph Series 27). World Health Organization, Geneva 1955
5. Cross AP, Singer B. Modelling the development of resistance of *Plasmodium falciparum* to antimalarial drugs. *Trans R Soc Trop Med Hyg* 1991; **85**: 349-355
6. Curtis CF, Otoo LN. A simple model of the build-up of resistance to mixtures of antimalarial drugs. *Trans R Soc Trop Med Hyg* 1986; **80**: 889-892
7. Ding GS. Recent studies on antimalarials in China: a review of literature since 1980. *Inter J. Exp Clin Chemother* 1988; **i**: 9-22
8. Hatton CS, Peto, TEA, Bunch C, Pasvol G, Russel SJ, Singer CR et al. Frequency of severe neutropenia associated with amodiaquine prophylaxis against malaria. *Lancet* 1986; **i**, 411-444
9. Lobel HO, Miani M, Eng T, et al. Long term malaria prophylaxis with weekly mefloquine. *Lancet* 1993; **341**: 848-851
10. Looareesuwan S, Charoenpan P, Ho M, White NJ, Karbwang J, Bunnag D, Harinasuta T. Fatal *Plasmodium falciparum* malaria after an inadequate response to quinine treatment. *J Infect Dis* 1990; **161**: 577-580

11. Nosten F, ter Kuile F, Chongsuphajaisiddhi T, Luxemburger C, Webster HK, Edstein M, Phaipun L, Thew KL, White NJ. Mefloquine-resistant falciparum malaria on the Thai-Burmese border. *Lancet* 1991; **337**: 1140-1143
12. Pukrittayakamee S, Supanaranond W, Looareesuwan S, Vanijanonta S, White NJ. Quinine in severe falciparum malaria: evidence of declining efficacy in Thailand. *Trans R Soc Trop Med Hyg* 1994; **88**(3):257-368
13. Qinghaosu Antimalaria Coordinating Group. Antimalarial studies on qinghaosu. *Chinese Med J* 1979; **92**: 811-816
14. Steffen R, Fuchs E, Schildknecht J, et al. Mefloquine compared with other malaria chemoprophylactic regimens in tourists visiting East Africa. *Lancet* 1993; **341**: 1299-1303
15. ter Kuile F, Nosten F, Thieren M, Luxemburger C, Edstein MD, Chongsuphajaisiddhi T, Phaipun L, Wester HK, White NJ, High dose mefloquine in the treatment of multi-drug resistant falciparum malaria. *J Infect Dis* 1992; **166**: 1393-1400
16. ter Kuile F, Dolan G, Nosten F, Edstein MD, Luxemburger C, Phaipun L, Chongsuphajaisiddhi T, Wester HK, White NJ, Halofantrine versus mefloquine in the treatment of multi-drug resistant falciparum malaria. *Lancet* 1993; **341**: 1044-1049
17. Thaithong S. Clones of different sensitivities in drug-resistant isolates of *Plasmodium falciparum*. *Bull WHO* 1983; **61**: 709-712
18. Watkins WM, Oloo JA. Lury JD, Mosoba M. Kariuki D, Mjomba M. et al. Efficacy of multiple-dose halofantrine in treatment of chloroquine-resistant falciparum malaria in children in Kenya. *Lancet* 1988a; **ii**: 247-250
19. Watkins WM, Brandling-Bennett AD, Nevill CG, Carter JY, Bariga DA, Howells RE, Koech DK. Chlorproguanil-dapsone for the treatment of non-severe *Plasmodium falciparum* malaria in Kenya: a pilot study. *Trans R Soc Trop Med Hyg* 1988b; **82**: 398-403.
20. Webster HK, Boudreau, EF, Pavanand K, Yongvanitchit K, Pang LW. Antimalarial drug susceptibility testing of *Plasmodium falciparum* in Thailand using a microdilution radioisotope method. *Am J Trop Med Hyg* 1985; **34**: 228-235
21. Wernsdorfer WH. The development and spread of drug-resistant malaria. *Parasitology Today* 1991; **7**: 297-303.
22. White NJ. Clinical pharmacokinetics of antimalarial drugs. *Clin Pharmacokinet* 1985; **10**: 187-215
23. White NJ. Antimalarial pharmacokinetics and treatment regimens. *Brit J Clin Pharmacol* 1992; **34**: 1-10.
24. Winstanley PA, Watkins WM. Pharmacology and parasitology: integrating experimental methods and approaches to falciparum malaria. *Brit J Clin Pharmacol* 1992; **33**: 575-582
25. World Health Organization. *Practical Chemotherapy of Malaria* (WHO Technical Report Series, 805). World Health Organization, Geneva. 1990(a).
26. World Health Organization. Severe and complicated malaria. *Trans R Soc Trop Med Hyg* 1990 (b); 84 Supp. 2: 1-65.

NEEDS IN DEVELOPING COUNTRIES: ONCHOCERCIASIS AND SURVEILLANCE FOR RESISTANCE TO IVERMECTIN

Kwablah Awadzi*

Introduction

Onchocerciasis is a filarial disease caused by *Onchocerca volvulus* and transmitted by blackflies of the genus *Simulium*. The disease is a chronic process punctuated by episodes of acute exacerbation. It produces much morbidity (pruritus, disfiguring skin lesions and weight loss) and is an important cause of blindness, especially in the savannah areas of tropical Africa, where socioeconomic consequences have been severe. An estimated 18 million people throughout most of tropical Africa, in the Americas (Guatemala, Venezuela, Ecuador, Colombia, Brazil and Mexico) and the Eastern Mediterranean (Sudan, Yemen and Saudi Arabia) are afflicted. At least 350 000 are blind and a further one million suffer from significant visual loss (WHO, 1987).

The bite of an infected female *Simulium* fly deposits infective larvae in the skin. These develop into adult male and female worms. The female worms produce microfilariae, which invade principally the skin and the eye. When taken up subsequently by the fly they develop into infective larvae, thus completing the cycle. The pathology of onchocerciasis results predominantly from the death of microfilariae in the skin, eyes, and lymph nodes and at other sites.

Drug treatment of onchocerciasis

Drugs act on both the microfilariae and the adult worms. Those available for treatment include suramin, diethylcarbamazine (DEC) and ivermectin. Suramin is curative while DEC and ivermectin are suppressive. Both DEC and suramin have been used for more than four decades. However, their administration in mass therapy is not recommended (WHO, 1987) on account of severe reactions (DEC) or toxicity (suramin), the need for close medical supervision, and lack of enthusiasm in the target communities.

Ivermectin (Mectizan) is a safe, effective, single-dose microfilaricide which is eminently suitable for community therapy. The standard dose is 150g/kg given once or twice a year. It achieves prolonged suppression of skin and ocular microfilariae by an additional, unique effect of blocking their release from the adult female worms. Repeated dosage may however be required indefinitely in the absence of *Simulium* control.

* Onchocerciasis Chemotherapy Research Centre, Hohoe, Ghana

Ivermectin has replaced DEC and further limited the indications for the use of suramin. Thus, for practical purposes, drug surveillance in onchocerciasis implies the monitoring of the adverse effects and of the development of resistance to ivermectin.

Resistance to anti-onchocercal drugs

Despite their use over several decades and in various dosage schedules (Hawking, 1978; Awadzi & Gilles, 1992), there is little evidence that *Onchocerca volvulus* has developed resistance to DEC or suramin. It is therefore unlikely that resistance will occur with ivermectin, which is given very infrequently, but the possibility can not be dismissed entirely, in view of its occurrence in veterinary practice by *Haemonchus contortus* (Echevarria & Trindade, 1989) and *Trichostrongylus colubriformis* (Giordano et al., 1988).

The development of significant resistance to ivermectin would be disastrous for onchocerciasis control, since mass ivermectin distribution can be used to supplement, or instead of, vector control (Remme et al., 1990; Greene, 1992). Therefore the sensitivity of *Onchocerca volvulus* to ivermectin must be monitored so that appropriate measures may be taken if required and also to develop a macrofilaricide suitable for mass treatment.

Monitoring sensitivity of *Onchocerca volvulus* to ivermectin

Two aspects need to be considered: a) the sensitivity of the microfilariae; and b) the ability of ivermectin to block the release of microfilariae from the adult female worms. Both can be investigated by direct and indirect means.

The microfilariae

Ivermectin causes rapid and near total reduction in skin microfilariae, followed by more gradual elimination of ocular parasites. This is accompanied by improvement in skin manifestations, ocular symptoms and anterior segment lesions, and a reduction in the incidence of optic nerve disease (Pacque et al., 1991; Dadzie *et al.*, 1991; Abiose *et al.*, 1993). Thus failure of increasing numbers of patients to benefit from ivermectin treatment or a less than expected reduction in skin microfilaria counts would suggest the development of resistance to the drug.

The sensitivity of microfilariae to ivermectin can be studied *in vitro* by the exposure of the parasite to graded concentrations of the drug and then determining their viability by suitable techniques, such as motility. A baseline sensitivity needs to be established which can then be monitored periodically. The requirement of increasing drug concentrations to obtain a given effect would then provide direct evidence of the development of resistance. In pursuance of this, baseline

data have been obtained by Townson *et al.*, (in press) for four geographical isolates of *O. volvulus* microfilariae obtained from Ghana (West African forest and savannah strains), Cameroon (West African forest strain), and Guatemala (Central American strain).

Ivermectin reduces the uptake of microfilariae and their development into infective larvae in the vector. This can be studied in feeding experiments on treated human volunteers (Cupp *et al.*, 1986, 1992; Trpis *et al.*, 1990; Chavasse & Davies, 1990). Failure to interrupt the uptake of microfilariae and to suppress their development into infective larvae on repeated dosage would suggest the development of resistance to ivermectin. The experiments however need to be carefully controlled as results may be influenced by a rapid return of microfilariae to the skin in areas of intense transmission (Remme *et al.*, 1990) and by population migration (De Sole & Remme, 1991; Cupp *et al.*, 1992). In non-endemic areas sensitivity can be studied by pretreatment of *O. volvulus* microfilariae with graded concentrations of ivermectin followed by their intrathoracic injection into surrogate vectors. The ability of these microfilariae to survive and develop into larval forms is then a measure of the degree of sensitivity to ivermectin (Tagboto *et al.*, in press). These *in vivo* experiments complement direct *in vitro* assessment of the sensitivity of *O. volvulus* to ivermectin.

The adult worms

The prolonged suppression of skin and ocular microfilarial counts is due to the blockage of their release from the adult female worms. A rapid return of skin microfilariae in a defined population would suggest resistance to the effect on the female worms. This can be confirmed directly by the examination of nodules excised from treated patients. The effects of intense transmission will have to be taken into account.

Surveillance for ivermectin resistance in developing countries

More than 17 million of the estimated 18 million people infected worldwide with *O. volvulus* live in tropical Africa, the worst endemic area being in the Volta river basin. Onchocerciasis is essentially a disease of rural populations in remote and sometimes inaccessible areas, beyond the last motorable road and the outermost health facility. Several countries lack trained medical and technical personnel. The distribution of ivermectin in some of these areas has been possible only through the efforts of the Onchocerciasis Control Programme (OCP), The River Blindness Foundation, Sight Savers and other non-governmental organizations. Surveillance for ivermectin resistance will require a similar effort on the part of the same or other organizations.

The monitoring of the effects of ivermectin in the skin and eye and the parasitological techniques involved in skin snipping and nodule

examination require highly trained personnel. The determination of ivermectin sensitivity by *in vitro* methods and the conduct of *in vivo* transmission experiments using *Simulium* species require specialized laboratories and personnel. Thus most such work has necessarily been done by visiting scientists from developed countries, aided by a handful of local experts. The transfer of technology and training to the endemic areas will be necessary if local scientists are to assume responsibility for these activities.

The major challenge to surveillance for ivermectin resistance is that it will not be undertaken because resistance is not expected to occur. However, a number of factors will tend to favour its occurrence. These include the use or projected use of repeated and high-dosage regimes in an attempt to obtain macrofilaricidal effects (Duke et al., 1990, 1991, 1992), and the unapproved use of ivermectin in endemic areas for conditions such as epilepsy and failure to thrive. Ivermectin is widely believed to be an anti-convulsant (Kipp et al., 1992), and failure to thrive has been attributed to 'worms', commonly *Ascaris*, the expulsion of which, during previous treatment, has left a lasting impression. There is also the regrettable practice of selling ivermectin as a cure for a wide spectrum of skin disorders.

Ivermectin is supplied free of charge by Merck for all who need it, and for as long as they need it. Monitoring for adverse effects is an essential part of distribution. Surveillance for the development of resistance, however improbable, should be instituted to ensure that the drug remains effective as long as it is needed.

References

Abiose, A., Jones, B.R., Cousens, S.N., Murdoch, I., Cassels-Brown, A., Babalola, O.E., Alexander, N.D.E., Nuhu, I., Evans, J., Ibrahim, U.F. & Mahmood, A.O. (1993). Reduction in incidence of optic nerve disease with annual ivermectin to control onchocerciasis. *Lancet*, **341**, 130-134.

Awadzi, K. & Gilles, H.M. (1992). Diethylcarbamazine in the treatment of patients with onchocerciasis. *British Journal of Clinical Pharmacology*. **34**, 282-288.

Chavasse, D.C. & Davies, J.B. (1990). The effect of ivermectin on the uptake and development of *O. volvulus* microfilariae in *S. damnosum* s.l *Acta Leidensia*, 59, No. 1 and 2, 227-230.

Cupp, E.W., Bernado, M.J., Kiszewski, A.E., Collins, R.C., Taylor, H.R., Aziz, M.A. & Greene, B.M. (1986). The effects of ivermectin on transmission of *Onchocerca volvulus*. *Science*, **231**, 740-742.

Cupp, E.W., Ochoa, J.O., Collins, R.C., Cupp, M.S., Gonzales-Peralta, C., Castro, J. & Zea-Flores, G. (1992). The effects of repetitive community-wide ivermectin treatment on transmission of *Onchocerca volvulus* in Guatemala. *American Journal of Tropical Medicine and Hygiene*. **47(2)**, 170-180

Dadzie, K.Y., Remme, J. & De Sole, G. (1991). Changes in ocular onchocerciasis after two rounds of community-based ivermectin treatment in a holo-endemic onchocerciasis focus. *Transactions of the Royal Society of Tropical Medicine and Hygiene*. **85**, 267-271.

De Sole, G. & Remme, J. (1991). Importance of migrants infected with *Onchocerca volvulus* in West Africa river valleys protected by 14 to 15 years of *Simulium* control. *Tropical Medicine and Parasitology*, **42**, 75-78

Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1990). Effects of multiple monthly doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene*, **43(6)**, 657-664.
Duke, B.O.L., Pacqué, M.C., Muñoz, B. Greene, B.M & Taylor, H.R. (1991). Viability of adult *Onchocerca volvulus* after six 2-weekly doses of ivermectin. *Bulletin of the World Health Organization*, **69(2)**, 163-168.
Duke, B.O.L., Zea-Flores, G., Castro, J., Cupp, E.W. & Muñoz, B. (1992). Effects of three-month doses of ivermectin on adult *Onchocerca volvulus*. *American Journal of Tropical Medicine and Hygiene*, **46(2)**, 189-194.
Echevarria, F.A.M. & Trindade, G.N. (1989). Antihelminthic resistance by *Haemonchus contortus* to ivermectin in Brazil: a preliminary report. *Veterinary record*, **124(6)**, 147-148.
Giordano, D.J., Tritschler, J.P. 2d & Colles, G.C. (1988). Selection of ivermectin-resistant *Trichostrongylus colubriformis* in lambs. *Veterinary parasitology*, **30(2)**, 139-148.
Greene, B.M. (1992). Modern medicine versus an ancient scourge: Progress toward control of onchocerciasis. *The Journal of Infectious Diseases*, **166**, 15-21.
Kipp, W., Burnham, G. & Kamugisha, J. (1992). Improvement in seizures after ivermectin. *Lancet*, **340**, 789-790.
Pacqué, M., Elmets, C., Dukuly, Z.D., Muñoz, B., White, A.T., Taylor, H.R. & Greene, B.M. (1991). Improvement in severe onchocercal skin disease after a single dose of ivermectin. *American Journal of Medicine*. **90**, 590-594.
Remme, J., De Sole, G., Dadzie, K.Y., Alley, E.S., Baker, R.H.A., Habbema, J.D.F., Plaisier, A.P., van Oortmarssen, G.J. & Samba, E.M. (1990). Large scale ivermectin distribution and its epidemiological consequences. *Acta Leidensia*, **59**, No. 1 and 2, 177-191.
Townson, S., Tagboto, S.K., Castro, J., Lujan, A., Awadzi, K. & Titanji, V.P. (1994). Comparison of the sensitivity of different geographical races of Onchocerca volvulus microfilariae to ivermectin: studies in vitro. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, **88(1)**, 101-106.
Trpis, M., Childs, J.E., Fryauff, D.J., Greene, B.M., Williams, P.N., Munoz, B.E. Pacque, M.C,. & Taylor, H.R. (1990). Effect of mass treatment of a human population with ivermectin on transmission of *Onchocerca volvulus* by *Simulium yahense* in Liberia, West Africa. *American Journal of Tropical Medicine and Hygiene*, **42(2)**, 148-156.
World Health Organization (1987), WHO Expert Committee on Onchocerciasis Third Report. *WHO Technical Report Series* No. 752 61-64.

NEEDS IN DEVELOPING COUNTRIES: SURVEILLANCE OF RESISTANCE TO ANTI-TUBERCULOSIS DRUGS

Paul Nunn* and Michael Felten*

I. Resistance to anti-tuberculosis drugs

This paper will summarize the current state of knowledge about resistance to anti-tuberculosis drugs in the developing world and discuss the critical role surveillance for drug resistance should play in the control of tuberculosis world-wide.

Anti-tuberculosis drug resistance — causes

What is generally understood by drug resistance is that a patient infected with resistant strains of *Mycobacterium tuberculosis* will fail to respond to treatment with the drug concerned. There are more precise and complex laboratory definitions[1,2], but they are less suitable for the purposes of this paper.

Resistance to anti-tuberculosis drugs is the inevitable result of poor management of tuberculosis control[3]. Poor management takes many forms, including the prescription of regimens with an insufficient number of drugs to which the patient's organisms are likely to be susceptible; inadequate dose or duration of therapy; or, most commonly, poor supervision of the patient's drug-taking, or poor supplies of drugs, resulting in drugs being taken irregularly. In the past, patients have taken much of the blame for poor compliance[4], but it is now recognized that tuberculosis services and their staff are not entirely innocent[5,6]. Either way, such deficiencies lead to patients acquiring resistance. If they then transmit the resistant organisms to their contacts, and if those contacts later develop tuberculosis also, then these latter cases are said to have primary resistance.

The impact of anti-tuberculosis drug resistance

Whatever tuberculosis programmes might do to cause drug resistance it is clear that drug resistance can also do considerable harm to tuberculosis treatment. Failure of treatment, which is commonly defined as the persistence of positive cultures for *M. tuberculosis* at the end of the treatment period, is more likely if the initial organisms were resistant. Moreover, the more potent the drug, and the more drugs to which an organism is resistant, the greater the risks of treatment failure. In the British Medical Research Council (BMRC) trials in Africa, Hong Kong and Singapore[7], of 11 patients with isolates resistant to

* Tuberculosis Programme, World Health Organization, Geneva

rifampicin, of whom 9 also had organisms resistant to one or more other drugs, 5 (45%) patients failed on treatment and a further 3 (27%) had a subsequent relapse. On the other hand, resistance to just isoniazid and/or streptomycin led to chemotherapy failure in only 12% of 264 patients.

Multi-drug resistance

In recent years attention has focused on multi-drug resistant (MDR) strains of *M. tuberculosis*. MDR strains are usually defined as those that are resistant to at least rifampicin and isoniazid, and often to other drugs as well. While occasional MDR strains have been isolated from time to time, it was outbreaks of MDR tuberculosis in the United States that brought MDR into the limelight[8-15]. These outbreaks were characterized by an association with the human immunodeficiency virus (HIV) and by an alarmingly high mortality of over 80%, despite the availability of a full range of reserve drugs. Widespread occurrence of MDR, especially primary MDR, would constitute a major threat to tuberculosis control, particularly to resource-poor countries, since effective treatment would become impossibly expensive[16].

However, there are grounds for some optimism. Rates of resistance do not rise inexorably. In Styblo's classic study in Kolin, ex-Czechoslovakia[17], the introduction of stronger control measures, especially supervision of all patients in hospital, ensured that almost all patients completed their therapy. The prevalence and incidence of resistance declined rapidly. Nevertheless, the most important measure against resistance is to ensure that it does not happen. This is achieved by making certain that all patients complete a full course of adequate treatment.

The role of HIV

The impact of HIV on drug resistance is not yet fully understood. The MDR outbreaks in the US suggest that HIV might be associated with resistance to anti-tuberculosis drugs. HIV-associated tuberculosis is some societies, such as part of the US[11] and Zaire[18], is associated with poorer adherence to therapy than that of patients with tuberculosis alone, and this could lead to the acquisition of resistance. HIV-infected tuberculosis patients are up to 20 times more likely than HIV-negative patients to have household contacts who are themselves HIV infected[19], and these contacts are particularly susceptible to contracting tuberculosis[20,21], which would likely be resistant if the source case also had resistant disease. However, the few studies, in the US[12,22], Haiti[23] and Africa[24,25], that have so far measured resistance levels in more representative cohorts of patients have not found an excess of resistance in the HIV-positive groups.

One can intuitively see that the impact of resistance will depend on the number and efficacy of the drugs available to treat tuberculosis. Six main drugs are in current use in the developing world: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S) and thiacetazone (T). The first three are the most essential. Streptomycin is given parenterally, and therefore constitutes a risk for HIV and hepatitis-B-virus transmission in those areas where sterilisation of injection equipment cannot be guaranteed. However, the risk has never been adequately quantified for tuberculosis control programmes with sufficient supplies and equipment. The cost of streptomycin has also increased considerably over the past few years. WHO does not therefore recommend it for use in areas with a high prevalence of HIV infection[26]. In addition, HIV infection has been shown to increase greatly the risk of severe, and potentially fatal, cutaneous hypersensitivity reactions in patients treated with thiacetazone[26-29]. It is therefore advised not to use this drug in patients known or suspected to be infected with HIV. The armamentarium available for the fight against resistant tubercle bacilli is thus somewhat reduced in areas of high HIV-prevalence.

Furthermore, withdrawal of thiacetazone might create resistance to more powerful drugs. If the commonly used regimen of 2SHRZ/6TH (an initial phase of 2 months of daily SHRZ, followed by 6 months of a continuation phase of T and H) is altered to 2EHRZ/6EH in some areas, then a proportion (unknown) of those patients with isoniazid resistance will, in effect, receive monotherapy in the continuation phase. Ethambutol resistance is therefore likely in a percentage (unknown) of patients so treated. Since the re-treatment regimen recommended by the International Union against Tuberculosis and Lung Disease[30] and WHO consists of 2SHRZE/HRZE/5HRE, the continuation phase will again, in effect, be monotherapy, this time with rifampicin. Rifampicin resistance in a proportion (again, unknown) is the likely result. This is the domino theory of resistance. Surveillance will, at the very least, help to determine the present unknowns in this scenario.

It is already clear however that new, effective, low-cost anti-tuberculosis drugs are urgently needed in the fight against tuberculosis in both the developing and the industrialized world.

II. Surveillance for resistance to anti-tuberculosis drugs

Current situation in the industrialized world

Until recently, very few countries, rich or poor, considered it necessary to carry out systematic surveillance for resistance to anti-tuberculosis drugs. The USA ceased surveillance in 1986, but resumed it in 1993. It was maintained in the industrialized world that the recommended treatment regimens were designed to succeed even in the presence of

resistance to one or two of the commonly used drugs; the minority of patients who failed to respond to treatment could be investigated for resistance as the need arose; surveillance was expensive, resources were limited, and, in any case, tuberculosis was disappearing fast. The occurrence of MDR, and the rising incidence of tuberculosis in many Western countries[31-33] due to HIV, immigration and the failure to maintain adequate health services in deprived inner cities, has led to a re-examination of this position.

Resource-poor countries

Likewise, in the developing world, in spite of a general failure to control tuberculosis, surveillance for drug resistance was not an issue until recently. Nevertheless, a number of countries such as Kenya[34], Tanzania[35] and Korea[3] conducted nationwide surveys at 5 or 10 year intervals to assess the extent of their tuberculosis problems. These generally included some representative information on drug resistance. In East Africa it was clearly not a major problem, with resistance to one or more drugs varying from 7-10% between 1964 and 1984. In Korea primary resistance to one or more drugs rose to 31% of isolates tested in 1960, but fell to 15% in 1990 with the introduction of improved tuberculosis control. Acquired resistance was as high as 75% in 1980, falling to 47% in 1990. Apart from these three studies, which also had their share of methodological problems, most published work has suffered from at least one of three major deficiencies which make interpretation difficult, if not impossible: selection bias (in favour of patients referred to major hospitals and thus more likely to have resistant disease), failure to distinguish clearly between those patients who had had previous treatment, or the use of non-standard or unclear laboratory methods. Our current level of ignorance of the scale and nature of drug resistance in the developing world is therefore profound, although we do know that HIV is plentiful, and MDR exists there (M. Kinyanjui and W. Githui, personal communication).

Aims of surveillance

The potential benefits of suitable surveillance for drug resistance are many. At an international level, surveillance could determine the geographical extent and severity of resistance in given countries or regions, and thus determine the need for major international changes in treatment policy. Such information would also determine the extent of the need for international research into new chemotherapeutic agents or new combinations of drugs. At a national level a surveillance system would provide a useful indicator of performance of a tuberculosis control programme and assessment of the need for changing current treatment policy, identify districts or health centres in need of support, and determine the risk factors for resistance.

But there are potential disadvantages. The diversion of scarce resources to resistance surveillance could jeopardize the essential tuberculosis control targets of curing 85% of all new smear-positive cases diagnosed, and finding 70% of all cases. However, it is in precisely those countries with poor programme performance that resistance could be predicted. National resources should then, perhaps, focus on achieving the targets, and donor agencies on resistance surveillance.

Recommendations

The Tuberculosis Programme of WHO has therefore developed a strategy which will determine the nature and extent of resistance to anti-tuberculosis drugs in regions of the developing world. Countries with viable tuberculosis-control programmes will be encouraged and assisted to develop their own surveillance system, using guidelines for surveillance drawn up by the Programme, which avoid the defects, mentioned above, of many previous resistance surveys. With the collaboration of the International Union against Tuberculosis and Lung Disease, it is intended to establish a network of supra-national reference laboratories to provide the quality control and standardization of susceptibility testing that will be essential for international comparison. At the same time, much-needed support will be given to national reference laboratories in developing countries to develop their own capacity for work on drug resistance.

Conclusion

Resistance to anti-tuberculosis drugs, and especially multi-drug resistance, is a major threat to tuberculosis control programmes. This danger is amplified by the presence of HIV. Our current state of knowledge about the extent and severity of resistance, especially in the developing world, is woefully inadequate. Surveillance for drug resistance is therefore needed in those countries with tuberculosis control programmes sufficiently developed to be able to support such a system. WHO is taking the initiative, together with the International Union against Tuberculosis and Lung Disease, to set up such a system.

References

1. Canetti, G, Fox W, Khomenko A, et al. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. *Bulletin of the World Health Organization.* 1969; **41**: 21-43.
2. Vareldzis B, Grosset J, de Kantos I, et al. Laboratory issues in drug-resistant tuberculosis: WHO Recommendations. *Tuberc Lung Dis* 1994; 75:1-7.
3. Kim S, Hong Y. Drug resistance of Mycobacterium tuberculosis in Korea. *Tuberc Lung Dis* 1992; **73**: 219-224.
4. Fox W. Compliance of patients and physicians: experience and lessons from tuberculosis. *Br Med J* 1983; **287**: 33-35.

5. Sumartojo E. When tuberculosis treatment fails: a social behavioral account of patient adherence. *Amer Rev Respir Dis* 1993; **147**: 1311-1320.
6. Rubel AJ, Garro LC. Social and cultural factors in the successful control of tuberculosis. *Pub Hlth Rep* 1992; **107**: 626-636.
7. Mitchison D, Nunn A. Influence of initial drug resistance on the response to short chemotherapy of pulmonary tuberculosis. *Amer Rev Respir Dis* 1986; **133**: 423-430.
8. Centers for Disease Control. Transmission of multidrug-resistance tuberculosis from an HIV-positive client in a residential substance-abuse treatment facility — Michigan. *MMWR* 1991; **40**: 129-131.
9. Centers for Disease Control. Nosocomial transmission of multi-drug resistant tuberculosis to health-care workers and HIV-infected patients in an urban hospital — Florida. *MMWR* 1990; **39**: 718-722.
10. Centers for Disease Control. Nosocomial transmission of multi-drug resistant tuberculosis to health-care workers and HIV-infected patients in an urban hospital — Florida. *MMWR* 1990; **39**: 718-722.
11. Pitchenik AE, Burr J, Laufer M, et al. Outbreaks of drug-resistant tuberculosis at AIDS centre. *Lancet* 1990; **336**: 440-441.
12. Chawla P, Klapper P, Kamholz S, Pollack A, Henrich A. Drug resistant tuberculosis in an urban population including patients at risk for Human Immunodeficiency Virus infection. *Amer Rev Respir Dis* 1992; **146**: 280-284.
13. Centers for Disease Control. Transmission of multidrug-resistant tuberculosis among immunocompromised persons in a correctional system — New York, 1991. *MMWR* 1992; **42**: 507-509.
14. Beck-Sagué C, Dooley S, Hutton M, et al. Hospital outbreak of multi-drug resistant *Mycobacterium tuberculosis* infections. *JAMA* 1992; **268**: 1280-1286.
15. Frieden T, Sterling T, Pablos-Mendex A, Kilburn J, Cauthen G, Dooley S. The emergence of drug-resistant tuberculosis in New York City. *N Eng J Med* 1993; **328**: 521-526.
16. Mahmoudi A, Iseman M. Pitfalls in the care of patients with tuberculosis: common errors and their association with the acquisition of drug resistance. *JAMA* 1993; **270**: 65-68.
17. Styblo K, Dankova D, Drapela J, et al. Epidemiological and clinical study of tuberculosis in the district of Kolin, Czechoslovakia: Report for the first 4 years of the study, 1961-64. *Bulletin of the World Health Organization* 1967; **37**: 819-874.
18. Perriens JH, Colebunders RL, Karahunga C, et al. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with "standard" chemotherapy in Kinshasa, Zaire. *Amer Rev Respir Dis* 1991; **144**: 750-755.
19. Nunn PP, Mungai M, Nyamwaya J, et al. The effect of human immunodeficiency virus type 1 on the infectiousness of tuberculosis. *Tuberc Lung Dis* 1994; **75:** 25-32.
20. Di Perri G, Cruciani M, Danzi MC, et al. Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet* 1989; **2**: 1502-1504.
21. Daley CL, Small PM, Schecter GF, et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. *N Engl J Med* 1992; **326**: 231-235.
22. Shafer RW, Chirgwin KD, Glatt AE, Dahdouh MA, Landesman SH, Suster B, HIV prevalence, immunosuppression, and drug resistance in patients with tuberculosis in an area endemic for AIDS. *AIDS* 1991; **5**: 399-405.
23. Long R, Scalcini M, Manfreda J, et al. Impact of human immunodeficiency virus type 1 on tuberculosis in rural Haiti. *Am Rev Respir Dis* 1991; **143**: 69-73.
24. Githui W, Nunn PP, Juma E, et al. Cohort study of HIV positive and HIV negative tuberculosis, Nairobi, Kenya: Comparison of bacteriological results. *Tuberc Lung Dis* 1992; **73**: 203-209.
25. Braun M, Kilburn J, Smithwick R, et al. HIV Infection and primary resistance to anti-tuberculosis drugs in Abidjan, Cote d'Ivoire. *AIDS* 1992; **6**: 1327-1330.

26. World Health Organization. Severe hypersensitivity reactions among HIV-seropositive patients with tuberculosis treated with thioacetazone. *Wkly Epidemiol Rec* 1992; **67**: 1-3.
27. Eriki PP, Okwera A, Aisu T, Morrissey AB, Ellner JJ. Daniel TM. The influence of human immunodeficiency virus infection on tuberculosis in Kampala, Uganda. *Am Rev Respir Dis* 1991; **143**: 185-187.
28. Pozniak AL, MacLeod G, Mahari M, Legg W, Weinberg J. The influence of HIV status on single and multiple drug reactions in Africa. *AIDS* 1992; **6**: 809-814.
29. Nunn P, Kibuga D, Gathua S, et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; **337**: 627-630.
30. Enarson D, Jentgens H, Oberhoffer M, et al. *Tuberculosis guide for high prevalence countries*. Paris, France: International Union against Tuberculosis and Lung Disease, 1991; 1-72.
31. Tuberculosis, final data — United States, 1986. *MMWR* 1988; **36**: 817-820.
32. World Health Organization. Secular trends of tuberculosis in Western Europe. *Wkly Epidemiol Rec* 1993; **68**: 65-72.
33. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in Western Europe. *Bulletin of the World Health Organization* 1993; **71**: 297-306.
34. Swai OB, Edwards EA, Thiong'o R, et al. Tuberculosis in Kenya 1984: A third national survey and a comparison with earlier surveys in 1964 and 1974. *Tubercle* 1989; **70**: 5-20.
35. Tanzanian/British Medical Research Council. Tuberculosis in Tanzania — a national survey of newly notified cases. *Tubercle* 1985; **66**: 161-178.

MONITORING THE SAFETY OF BIOLOGICAL PRODUCTS

Susan S. Ellenberg*

Biological products

The definition of a biological is given in the US Code of Federal Regulations (600.3(R)): A biological product is any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment, or cure of diseases or injuries of man. Biological products are regulated by the Centre for Biologics Evaluation and Research (CBER), while drugs and other medical interventions are regulated by the Center for Drug Evaluation and Research or the Center for Devices and Radiologic Health. A list of some of the types of product that CBER regulates is given in Table 1. Some, such as blood

Table 1. ***Types of biological product regulated by CBER***

Allergenic extracts	Diagnostic agents
Antitoxins	Gene therapies
Cytokines	Growth factors
Blood derivates for therapy	Monoclonal antibodies
Blood products for replacement	Thrombolytic agents
Coagulation factors	Vaccines

derivatives, are traditional products that have been available for many years; others represent newer products of biotechnology. ("Biotechnology" refers primarily to recombinant DNA technology-produced products, monoclonal antibodies, and some somatic-cell and gene therapies and vaccines.) The number of investigational biological products has increased rapidly over the last decade.

The special case of vaccines

Some of the most important types of product regulated by the Center for Biologics are vaccines. The surveillance system for vaccines is separate from that for biological therapeutic products. It is called the Vaccine Adverse Event Reporting System, and it is implemented by the FDA together with the Centers for Disease Control and Prevention, in Atlanta, Georgia. The system has been in operation only since November 1990. The reporting form is specific to the system; the

* Division of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research, US Food and Drug Administration

MedWatch form recently introduced by the FDA for reporting adverse events in connection with therapeutic products is not used for reports on vaccines. In contrast to therapeutic products, on which most adverse-experience reports are submitted by manufacturers, more than 50% of the reports on adverse events associated with vaccine use are submitted direct to the FDA by health professionals. This is one of a number of differences between monitoring vaccines and monitoring therapeutics. One major difference is that vaccines are given to healthy individuals, mostly children. The "mind-set" on the acceptability of adverse events in this population is quite different from that on therapeutic products. The assessment of causality in regard to vaccines is even more difficult than with drugs because, when immunizations are given universally, almost any kind of adverse event that happens to an infant during the first year of life will be not too far removed in time from a vaccination. Experts in this area believe that a very, very small proportion of the serious adverse events that are reported are truly caused by the vaccine; such events are reported primarily because of temporal coincidence. This is a difficult issue to study, however, because the rates of exposure to the vaccines are so high. In a sense, with vaccine adverse-event-reporting we have problems of over-reporting as well as under-reporting, because most of the reports probably do not reflect vaccine-induced events.

The regulation of biological products

At present there is no formal regulation requiring the reporting of adverse events or biologicals; biological adverse events have been reported voluntarily by manufacturers for some time. CBER will soon issue its adverse-event-reporting regulations. Requirement for 15-day alert reports, periodic reports, and increased-frequency alert reports will be specified. We shall also be collecting data on the amount of each product distributed. These data will provide a crude estimate of the number of individuals exposed to a product, permitting calculation of bounds on rates of adverse events. There is a strong intent, in both the Center for Biologics and the Center for Drugs, to move toward international standards of reporting as initiated by CIOMS and the International Conference on Harmonization (ICH); while for technical reasons this will not happen immediately, it is planned to bring the regulations for both Centers into harmonization simultaneously with the recommendations of these groups.

The Center for Biologics participates in the MedWatch programme along with the Center for Drugs and the Center for Devices and Radiological Health. The forms are received centrally, and rapid feedback of direct reports (that is, reports sent direct to the FDA for health professionals, parents, consumers, etc.) is provided to the manufacturers. The MedWatch Programme has been widely pub-

licized, and we hope it is going to increase the level of reporting, particularly of serious, unexpected events.

Special challenges for the monitoring of biological therapeutic products

These are in four different areas:

(i) *The patient populations that receive biological products*
Patient populations for biological products tend to have serious and complex disease. In many instances it is difficult to distinguish the effect of the drug from the effect of the disease. Also, because the patients are often quite ill, they are usually taking a variety of medications, which will complicate interpretation and assessment of causality for the events reported. Of course, not all biological therapies are administered in such contexts, and certainly some drug or chemical therapies also are given to such populations; but it is probably true that, on average, this is more of a problem for biologics.

(ii) *The magnitude of the drug development programmes*
Drug development programmes are often limited in size because for many indications the population is quite limited; for example, studies of genetic disorders, rare cancers, and certain neurological diseases such as amyotropic lateral sclerosis. Biological therapies tend to be developed in these smaller but seriously ill populations, because with serious, often life-threatening diseases there is more leeway for moving promising products rapidly through the drug approval process. (There is now a special programme called "Accelerated Approval", which allows us to do just that in these special situations.) A practical problem is that many of the new products, particularly biotechnology products, are being developed by small companies with limited resources. We have the difficult task of trying to encourage the development of exciting new products in the creative atmosphere of these small companies without compromising the standards that we require for proof of efficacy and safety.

(ii) *The broad spectrum of activity of most biological products*
Biologicals are pleiotropic. Biologics can have many different kinds of effect, some of which may well be adverse. Many unusual types of adverse event — cancers, neurological and psychiatric problems, endocrine disorders — have probably been associated with biological therapies to a greater proportional extent than with other types of therapeutic product. It is difficult to predict what is going to happen when these products are put into human beings, so that there is a need to monitor for both acute and long-term effects. Many biologicals are what we call biological response modifiers: they are directed not at the disease itself but at the body's biological response to the disease. Therefore, the disease

process may continue, or even accelerate or become more severe. In addition, biologicals are immunogenic. Immune-complex disease has occurred with certain biological products. There is also an increased risk of some common adverse events such as allergic reactions that are related to the immune system.

(iv) Some manufacturing issues

The complexity of the manufacturing process for these products raises special issues for quality control with regard to the purity of the product, storage issues, stability, and sterility. The surveillance is lot-specific; that is, each lot must undergo certain kinds of testing and be individually approved for release. Further, the lot is something that we have to take into account as we monitor the adverse-event reports received for products after they are put on the market.

Conclusion

I have tried to raise some of the challenges that confront surveillance programmes for biological products. Despite the differences between biologics and drugs, there seems no reason why the general approach to monitoring should not be the same for biologics as for other therapeutics. The increased efforts that are being made toward international harmonization of adverse-event reporting are going to be important to the development of more efficient surveillance programmes.

Acknowledgements

I acknowledge helpful discussions with my colleagues, including Dr Kathryn Zoon, Director of the Center for Biologics Evaluation and Research; Dr Jay Siegel and Mary Jane Walling, also from the Center for Biologics; and Edward Bortnichak and Dagmar Oette from Ciba-Geigy.

NEW APPROACHES TO PHARMACOVIGILANCE AND ALTERNATIVE STRATEGIES

Bengt-Erik Wiholm*

I am honoured to have been invited to this 25th anniversary, and to have been charged with looking into the crystal ball and to suggest new approaches to pharmacovigilance. However, to those who know history new thoughts are rare. Some 3,700 years ago King Hammurabi decreed that any physician who hurt his patients through treatment should be severely punished and today lawyers uphold that tradition. Hippocrates introduced a code of ethics in medicine and we should be wise to follow it. Paracelsus in 1538 introduced the concept of dose-effect relationship but we still lack good data in this area for most medicines. Longmoore (1978) described salicylate toxicity in a case-series study, and although this knowledge has been rediscovered many times aspirin is still an over-the-counter drug. Mendel in the 19th century described the laws of genetic variation and now we are slowly accepting the concept in drug metabolism. A registry for drug-induced diseases was instituted in the United States in 1952 and now I shall suggest it again as one of the methods of the future.

The scenario for the rest of the '90s in drug development and regulation is influenced by several major factors. The internationalization of drug development and marketing, as well as the rapid expansion of international cooperation between drug regulatory agencies, including moves towards supranational decision-making, e.g. the European Commission, provide a scenario in which new medicines will be introduced on to the world market at more or less the same time in all countries.

This evolution is essentially rational with regard to development costs and the need for rapid access to effective new medicines. However, it also results in rapid and massive exposure of patients to medicines with inadequate evidence of safety. It is widely recognized that the clinical trials programmes have not been sufficient to prove safety, because of their inherent limitations. The result has been that during the last 20 years 3% of new drugs have been withdrawn and another 10% have had to be seriously limited in their use because of adverse effects.

Imporovements in the design, methodology and monitoring of clinical trials and the possibilities of integrating results from different single trials mean that today frequent short- and medium-term adverse drug reactions to a new chemical entity are well characterized in the populations studied, prior to general marketing.

* Medical Products Agency, Uppsala Sweden.

The challenge that we face is how best to follow up all these new medicines to ensure their safety in clinical practice — that is, in patients who differ in many important aspects from those on which the medicine was tested, such as ethnic origin, age distribution, disease patterns, concomitant therapy, and therapeutic environment.

Our common problem thus relates more to the identification of uncommon reactions, reactions induced by long-term treatment, and problems emerging as a result of new patient groups being treated — e.g., increased susceptibility or new interactions.

Experience shows that very many of the problems associated with new medicines surface only several years after their introduction. It took 30 years to detect the association between aminopyrine and agranulocytosis, and more than 100 years to detect the association between salicylates and Reye's syndrome. In a recent survey performed by Professor Auriche and Dr Spriet-Pourra in France, it was shown that the median market-life for new chemical entities withdrawn from the European market during the period 1982-86 was nine years. Only 15% of these products were two years or less of the market.

Clearly some of the problems were known long before the product was finally withdrawn, and some of the withdrawals may be questionable. The point to make, however, is that new problems tend to surface also long after the introduction of the medicines.

The evaluation of new potential adverse effects of medicines is a multifaceted and complicated procedure, which includes the following steps:

- Detection and hypothesis generation
- Verification or refutation of the hypothesis
- Quantification — estimate of relative and attributable risk
- Exploration of mechanisms
- Identification of possible high-risk populations and the search for markers of increased susceptibility
- Evaluation of the clinical impact of the reaction on the individual and the population
- Identification of possible preventive strategies — including, as a last resort, regulation of the use of the medicines
- Information to the prescribers, the patients and those concerned in the medical community.

The responsibility of this task should be shared between the producers, the regulators, the scientific community, the prescribers and the users of the products. There is no single method which can encompass and answer all these necessary questions. Therefore, we must build up a portfolio of supplementary methods, each designed to handle most effectively the different parts of the safety evaluation.

Specific suggestions for detection

We need to develop rapidly the signals of new potential adverse effects of new medicines. Therefore, the reporting systems have to become more efficient. This can be done by increasing the sensitivity and the specificity of the spontaneous reporting systems or by creating new mechanisms. Unfortunately, the kind of automated signal generation that Dr Mann suggests is yet a long time ahead for most societies. Until then I hold that motivation and imagination are key elements in the development of efficient reporting systems, but neither can be introduced and maintained by legislation and regulation.

In an area where progress is dominated by these human characteristics, I believe that the most profitable approach is to increase the size of the carrot instead of the use of the whip. In Sweden we have taken this path, and by decentralizing the reporting to a regional level and linking it with the drug information units we have obtained a 43% increase in the reporting rate — from some 300 to 550 reports/million inhabitants/year. The quality of the reports also has improved markedly as most of the reports of potential new reactions have contained copies of case records, laboratory lists, etc. Similar experiences have been reported from France, Spain and Thailand.

This could not have been done in an environment where the reporting was directed to drug companies. because in most countries manufacturers cannot store the identities of patients and it is therefore more or less impossible to follow up on the single cases — especially since the manufacturers cannot force the clinicians to give them supplementary background information.

Specific suggestions for quantification

In the process of verification, quantification is a key issue. Spontaneous reporting systems have several weaknesses in this respect. The most important drawback is that ADRs by nature are not unique events but rather mimic diseases from other causes, and that several diseases, such as rheumatoid arthritis, can induce symptoms that are also often seen as adverse drug reactions. The only way to solve these issues is by adopting an epidemiological approach, thereby creating comparative data on the incidence of the occurrence of the symptom in people exposed and not exposed to the drug of interest. This can be done by two different approaches: the cohort and the case-control approach.

They differ mainly in that the cohort approach is the more efficient for describing the total risk profile of one medicine as compared with no treatment or an alternative treatment, whereas the case-control design is the more efficient for comparing the risk of a certain type of reaction with different medicines. For rare reactions the case-control approach is almost always the more efficient, provided the exposure is reasonably common. This poses a special problem for new drugs before

they are widely used, and to meet this situation Professor Inman created a new approach — the Prescription Event Monitoring Scheme — which has much potential if further developed. However, traditional postmarketing monitoring by means of unfocused cohorts is rarely cost-effective, but the New Zealand scheme, in which initial patients are tagged but not followed up unless a signal arises, is probably a cost-effective solution that should be further explored.

However, not too uncommonly the outcome under study is rare and exposure to the medicine is also rare. Then, as exemplified by acetazolamide and aplastic anaemia, and dapsone and agranulocytosis, neither of the above methods can work at an affordable cost or within an acceptable time. In these circumstances the only practical way to get a rough estimate of the frequency of the problem is good collection of case information in spontaneous reporting systems or disease registers, and the intelligent use of sales and prescription data. One advantage of disease registers is that they involve clinical specialists, which guarantees the necessary diagnostic precision, and therefore may provide the foundation for diagnostic developments such as those reported yesterday at the first meeting of the European Society of Pharmacovigilance.

Most often, however, information from controls is needed to make valid comparisons, and a case-control design is the most effective way of analysing a signal. Such studies can be done in several ways and in countries with limited economic resources. In Barcelona, Professor Laporte is running an emergency-room case-control survey, which can serve as a model. Also, problems linked to non-compliance and drug resistance could probably be studied on a similar basis in developing countries, around sentinel posts where patients seek medical care.

In the previously mentioned survey of drug withdrawals it was found that the reasons for withdrawing medicines were not only of type B, and being rare they were also concentrated in a limited number of clinical expressions. Of 79 withdrawals due to clinical adverse reactions, about 75% related to serious skin reactions, blood dyscrasias, liver damage, general allergic reactions, kidney failure and neurological reactions. Therefore, a scheme has been suggested, based on an international network of case-control surveillance covering those serious but rare diseases that can be caused by many drugs and that often cause drug withdrawal.

Such a scheme would meet most demands of a future pharmacovigilance system as it would yield continuous and timely information on the clinical expression of serious reactions to old and new drugs. Moreover, it would yield risk estimates of sufficient precision to make valid risk comparisons between existing and new medicines. The system could also form a basis for mechanistic research and a data-bank for DNA from patients experiencing serious idiosyncratic reactions, which in the future could help in elucidating the mechanisms and risk factors

for such reactions. Moreover, a data-base on detailed drug intake in relation to life-style habits and diseases from the controls would permit international comparison of the rationality of drug use. With a large common pool of controls such a system could easily tackle other types of signals as they come — e.g., *torsade de points* arrhythmias and the use of antihistamines.

During the last 20 years a number of multi-purpose record-linkage data-bases have been created, first in North America but now increasingly also in Europe. Such data-bases, if properly used, can be very valuable. They can be used to make quick but rough analyses of potential problems in emergencies, but because of selection bias and misclassification problems they are not well suited for detailed studies of adverse reactions that can be elicited by sporadic drug intake. For studies of long-term risks and teratogenicity they should be of immense value in the future unless the new laws on the confidentiality of medical data contemplated by the European Parliament and the European Commission will make use of such data-banks impossible.

Funding of drug-safety studies

Many countries are becoming increasingly market-oriented and have a declining amount of society-dominated research funds. The pharmaceutical companies have money but are naturally oriented more to products than to problems. Society has the problem but no funds are allocated. For example, it is quite unacceptable that we spend millions of dollars on lipid-lowering drugs without knowing whether they save lives or only lower a biochemical marker. Thus, we need to create some common funds for society-oriented drug-safety problems, and why not place these under CIOMS auspices?

SESSION V

ACCESS TO INFORMATION: PATIENTS AND COMMUNITIES

Chairman: Robert J. Levine

ACCESS TO INFORMATION: PATIENTS AND COMMUNITIES

Introduction

Robert J. Levine

Dr Bankowski has asked me to open this session with some remarks which reflect my perspectives as an ethicist and as a clinician. Since time is short I will limit my remarks to some suggestions about the scope of our agenda for this session. They will be a sort of impressionistic overview of the potential scope of our discussions on access to information. We may, for example, talk about providing information to patients and to research subjects. Much of this discussion has gone on here at CIOMS earlier under the topic of informed consent, and for those who would like to see a good bit of writing relevant to that topic it appears not only in the 1993 CIOMS publication, *International Ethical Guidelines for Biomedical Research Involving Human Subjects,* which Dr Bryant mentioned, but also in the 1991 CIOMS publication, *International Guidelines for Ethical Review of Epidemiological Studies.*

Another topic we might consider is conditions under which transmission of information to the public might be either withheld or delayed. Sir William Asscher, when he spoke of his seven deadly sins, identified one as ambition. Ambition might stand in the way of somebody publishing a case report. As he put it, the one who first identified an adverse drug reaction might want to wait to publish a report on it until he or she found another two or three so that the report would become a full-fledged publication. On a much larger scale we sometimes see enforcement of what has come to be the Ingelfinger Rule standing in the way of timely delivery of information to the public, as journals such as the New England Journal of Medicine have held up, for varying periods of time, publication of the reports of important clinical trials or case-control studies.

We might also consider the way in which access to information by epidemiologists may be impeded by legal or ethical barriers or by the actions of research ethics committees. For example, yesterday John Dunne spoke about the inability to get into contact with patients because of policies designed to protect the privacy of patients. I have also noticed of late that the development of privacy legislation in Europe threatens the destruction of large areas of epidemiology, including the destruction of registries that have been maintained by epidemiologists to do very important work. In my view, almost all of the interpretations of the ethics and law of privacy that lead to barriers to the conduct of epidemiological work are based upon some ill-considered reasoning.

Another topic we might consider is whether steps might be taken to prevent the premature release of preliminary information, or in some cases preliminary speculations, to the public. Not only does this result in tragedies like what occurred with pertussis vaccine, as described yerterday by Professor Rawlins, but sometimes it makes it very difficult to begin a randomized clinical trial when people, including members of research ethics committees, hold the belief that it is already known that a drug is effective or ineffective, or more effective than whatever it is being compared with. And the final case I will mention is that called first to our attention by Dr Phillips-Howard, the deprivation of people in communities in developing countries — they are deprived perhaps unjustly, I believe unjustly, of access to such benefits as new drugs, and access to knowledge about adverse drug reactions, and I think that this could also become part of our agenda this afternoon.

LEGAL ASPECTS OF ACCESS TO INFORMATION ON DRUG REACTIONS

Bernard M. Dickens*

Introduction

Legal concerns in drug surveillance studies arise at individual, public and institutional levels. Individual interests concern the conventional legal issues of patients' adequately informed, non-coerced and not unduly induced decisions about whether to accept drugs they are offered for therapeutic or preventive care, and preservation of personal confidentiality. Information about prospective treatments and uses of data serves patients' autonomous choices in care. The legal duty of disclosure of information about therapies is based on legal criteria of what responsible health-care providers know and reasonably ought to know about the effectiveness, side-effects, contraindications and, for instance, limits of prevailing knowledge of administration of drugs they recommend or are willing to prescribe. A limit of knowledge may be due to the lack of long-term follow-up studies of populations of patients to whom a drug has been administered. These are often described as post-marketing surveillance studies or Phase IV studies.[1]

Public interests arise from considerations of public safety and drug licensing authorities' need to make benefit-to-risk assessment in determining whether a drug is safe for marketing. Extreme caution will deny for many years the benefit of a drug to those it could help, and compel exhaustive pre-marketing tests that will drive up research and development costs, which pharmaceutical companies will reflect in their prices for drugs when they are approved for marketing. In both developed and developing countries, such costs may fall on government health care systems when they supply therapeutic drugs or subsidize their costs. Speed of approval of licensure of a drug may expose to undue risks patients for whom long-term follow-up studies would show the drug to be ineffective or contraindicated. A judicious middle path is to approve licensure on reasonable demonstration of a drug's effectiveness and safety, but to make marketing conditional on post-marketing surveillance studies and diligent reporting and analysis of adverse drug reactions, which may include apparent ineffectiveness as well as untoward outcomes of use of the drug.

Institutional interests arise when investigators who develop or administer drugs or are responsible for post-marketing studies hold positions in universities, hospital research institutes or similar institutions: their contracts of employment will often require or imply the application of ethical guidelines for research involving human

* Professor of Law and Medicine, Faculty of Law, Faculty of Medicine and Centre for Bioethics, University of Toronto, Toronto, Canada M5S 2C5

subjects as individuals or populations. These private contractual agreements reinforce or provide legal enforceability of ethical guidelines for the conduct of research on individual human subjects and populations, and indeed on the use of animals in research.

This chapter identifies three issues that require legal resolution in drug post-marketing surveillance studies, and concludes with observations on how courts are likely to approach the employment of knowledge that arises or ought to arise from such studies.

1. The conflict between confidentiality and the right to know

Patients traditionally have been recognized to enjoy legal rights of confidentiality regarding not only the outcome of their medical treatment, but also the conditions for which treatment is sought and applied. Rights may be based in law on contracts for medical services, duties of care that physicians assume on entering a relationship of doctor and patients, whether or not the relation is based on contract and, for instance, on the fiduciary duty the physician owes the patient. This duty is to protect the patient's confidences and employ information arising from the relation only in the patient's best interests or with the patient's prior informed and free agreement. Patients' rights are not absolute, and legal systems recognize that, on occasion, higher interests may prevail that mandate, justify or excuse limited disclosures, often to public agencies that must themselves guard information that they receive. Public health laws often compel or justify disclosures, such as when notifiable diseases are diagnosed. If post-marketing surveillance studies fall under the protection of explicit legislation, this will usually prevail over patients' individual claims of confidentiality.

Surveillance studies rarely enjoy this level of protection. The legal duty to report adverse drug reactions may have a legislated basis, but reports may be statistical and informational, not naming or otherwise identifying individual patients. If a physician makes it a condition of administering a drug that the patient consent to identifiable outcome data subsequently being made available to, for instance, the drug manufacturer, consenting patients may accordingly be held in law to have waived or surrendered their rights to confidentiality to that extent. However, when patients feel they have no option but to accept such conditions in order to obtain drugs essential to their care, courts may find the consent to have been coerced, and to be an unenforceable but severable condition of patients' acquisition of treatment. Anonymous single case reports to manufacturers may be upheld, since patients' confidentiality is not then involved.

Some medical disorders may raise patients' special apprehensions about identifiable disclosures occurring, such as infections with a sexually transmitted disease or the AIDS virus, malignancies, sexual dysfunctions including infertility, and psychiatric disorders. Even when

disclosure of a disorder is not sensitive, stigmatizing or otherwise prejudicial, patients are entitled to preservation of their privacy. There is no difference between disclosures that patients suffer from named disorders that are being treated and disclosures that certain conditions such as depression, impotence or dependency have been caused by drug treatments, or indeed that some such conditions have been successfully treated. Patients are entitled in principle to control what information about them is made available to others, and not to have their names given to drug companies or independent investigators for surveillance studies, which some investigators might want to pursue for decades or generations following initial drug administration. Patients are also entitled not to be pressured or unduly induced to consent to such disclosure of their names, or to fear prejudice in care if they decline to consent.

As against this, however, patients for whose care a drug may be appropriate have a strong interest in their physicians and the manufacturers who advise prescribing physicians learning as much as possible about the drug, including its long-term effects, and having access to earlier users' medical information for that purpose. Acquisition of data sets and anonymous anecdotes may be insufficient, since precision in safe prescription may depend on determination of whether an earlier patient's adverse outcome was due to the drug, an unrelated cause or the interaction of the drug with a predisposing factor, such as genetic characteristics or, for instance, other earlier or concurrent drug treatments. Clinical scrutiny of the patient who experienced the single-case adverse outcome may be the essential condition of future safe prescription of the drug.

A prospective patient's interest in this level of study of other patients' medical experiences is shared and amplified by national drug licensing or importing authorities that have approved the drug for prescription. As guardians of the public welfare in the safe prescription of drugs, accountable to the public for their diligence and efficiency, they want harmful effects that may be due to an approved drug to be probed. The manufacturers and commercial promoters and distributors of the product are similarly interested in its demonstrable effects and contraindications that single-case examinations and wider surveillance studies may provide.

Patients' rights to protection of their personal data may have been founded on customary or judge-made laws, but a number of jurisdictions have now protected the right to confidentiality by legislation on confidentiality itself or by wider laws on patients' rights and health professionals' obligations. However, legislatures may find that they are also interested in patients' medical records being available to governmental and private agencies, such as pharmaceutical manufacturers, for the purpose of post-marketing surveillance studies. The balance between the competing claims of individual

confidentiality, on the one hand, and, on the other, the public interest in appropriate disclosures of anonymous and identifiable data may be struck on grounds of public policy by governmental and legislative agencies or by the courts. Legislation that permits agencies to obtain identifiable information without patients' consent or knowledge may also have to impose strong obligations of data protection on such agencies in order to receive judicial or public approval.

Where surveillance studies cannot be conducted by non-consensual access to patients' identifiable medical records, courts will not be able to impose duties of conducting comprehensive follow-up studies on physicians or drug manufacturers in litigation by patients attributing harmful outcomes to drugs. The extent to which courts require expenditures on consensual or non-consensual surveillance studies will be a matter of judicial policy influenced by economic factors, degrees of harm and risk, and judicial concern with drug pricing practices. The background law will determine the standard of vigilance to outcomes of drug use that physicians and drug manufacturers will be expected to observe. If governments or legislatures want a higher standard, or a standard more respectful of individual confidences, they may promote and enact legislation for this purpose.

2. Levels of information disclosure in surveillance studies

Patients may be made aware of others' interests in the results of their taking of prescribed drugs at the time the drugs are recommended or administered, or, more usually, after they have taken the drugs and effects have been produced, such as adverse drug reactions. This raises the legal question of their consent to involvement in studies, and in particular what level of information must be disclosed to them for their agreement to participation to meet legal standards.

Physicians' compilation of aggregated statistics of results of their care of their own patients will not usually be considered to be human research. Informing drug companies that given volumes or dosages of a drug were prescribed to a total number of patients and that a percentage or number responded favourably, that a percentage or number did not appear to respond at all, and that there was a percentage or number of adverse reactions, will not involve individual patients in research as such. Their care will conform to clinical practice directed solely to their welfare, and data resulting from their care will be presented anonymously. No examination or monitoring that exceeds or departs from that therapeutically indicated will be undertaken, so that neither patients' management nor confidentiality will be affected. This is accordingly not research that involves human subjects in any way that requires individual patients' consent. Information is used for a purpose for which it is not directly given, namely to contribute to the comparative compilation, but patients will

know in advance that their physicians have access to their medical records.

When some departure from or variation of routine management of a patient is proposed for the sake of a surveillance study, however, the patient's consent will usually be legally required, or authorization from an appropriate source regarding patients unable to give legally effective consent for themselves. The law reflects the ethical principle that standards of disclosure for consent in therapeutic practice and in research are not necessarily the same.[2] The purpose of disclosure in both cases is to contribute to individual autonomy of patients and subjects respectively, but in therapy there is the so-called "therapeutic privilege" of non-disclosure of information that routinely should be given, because it is feared, in clinical judgment, that it might jeopardize success of a proposed method of therapeutic care for a particular patient. The privilege has been formulated in a variety of ways by legislatures and courts,[3] but its essence is that patients' care should not be compromised by disclosures that might induce physical or psychological reactions that would impair their therapy or welfare. It is not a sufficient ground for non-disclosure that a physician simply fears that relevant information would deter a patient from making a decision the physician considers best advised.

Uncritical language sometimes describes the law as requiring patients' "fully" informed decisions on medical treatment, but the legal standard is one of adequacy. Decisions on both therapy and research must be adequately informed, but criteria of adequacy require more disclosures for research than for therapeutic recommendations. Adequately informed decisions are responses to disclosures of information material to the choices that patients have to make. Patients who are competent to exercise choice are presumed to be possessed of common intelligence and to understand, for instance, that not every proposed treatment is guaranteed to be effective, or without risk of adverse effect.

Accordingly, the law does not hold physicians to guarantee the effectiveness of treatments they recommend, or to promise that there will be no idiosyncratic or reasonably unpredictable adverse reaction. For instance, courts do not require disclosure of the risk of a routine blood transfusion transmitting hepatitis B, because the risk, although real, is too low to be material to the choice to be made by a patient for whom transfusion is therapeutically indicated. Indeed, courts have held that over-informing is as much malpractice as inadequately informing, since both may deny patients their autonomous right to exercise choice on the basis of relevant information. In some legal systems this means information that is material to the choice of a reasonable person in the patient's circumstances; in others it means information that physicians usually provide. Whatever the legal orientation, however, courts do not require that everything known about a proposed treatment be

disclosed, but that physicians will determine on reasonable grounds how much of what is known, and unknown, should be disclosed, and what routinely will not be disclosed unless a particular patient makes the information material, notably by asking a relevant question.

The "therapeutic privilege" of non-disclosure concerns information that routinely should be given according to the legal test of materiality or professional practice, but that an attending physician decides should not be given to a particular patient on the basis of that patient's personality, characteristics and, for instance, history, because it might compromise the patient's care. Courts treat therapeutic privilege restrictively, for fear that it may subvert not only a patient's autonomy but the general rule of disclosure. The burden of establishing the legal propriety of exercise of non-disclosure, for instance, falls on the physician, who must justify the decision not to give information that routinely should be given. It follows that where an intervention into a patient's treatment or confidentiality is requested for a surveillance study and not advised on therapeutic grounds, there is in law no therapeutic privilege of non-disclosure.

Controversy continues to surround innovative treatment, such as administration of an unapproved drug or of an approved drug on an untested indication that a clinician advises on therapeutic grounds. The recommendation may be, for instance, because of the novel combination of medical features presented by a patient or because standard therapeutic options have been discredited or are clinically contra-indicated. Unproven treatments may be proposed on therapeutic grounds with preservation of the therapeutic privilege, even though the treatment will produce an outcome that will be of secondary but significant interest and service to the research community. Descriptions such as therapeutic research are unhelpful in distinguishing therapeutic treatment from instances of human experimentation or research, as is the medical professional practice of describing unproven procedures undertaken to address patients' health problems as clinical experimentation.

It may be observed, however, that when treatment and subsequent monitoring are undertaken on an exclusively therapeutic basis but clinical outcome data will contribute to research knowledge, for instance through extraction of data from the medical file, the research is distinguishable from the therapy. Information for consent to inspection of the medical record by investigators does not have to address any intervention that was part of the therapy and follow-up care unaffected by any intention to produce research data, whether the intention arose in advance of the therapeutic recommendation or subsequently.

Post-marketing surveillance studies are not essential to therapeutic care of individual patients, although designed to benefit the population of present and prospective patients in general. They rank as research, even though they may be limited to secondary use of outcome data

from therapeutic treatment, and information must be fuller than is required for therapy. For instance, risks of which people of common intelligence may be unaware but that are inconsequential in proportion to the prospective benefit of therapeutic treatments, such as of contracting hepatitis B from an essential blood transfusion during or following surgery, need not be disclosed. However, the same risks should be disclosed when a subject is invited to participate in the medical procedure for non-therapeutic reasons.

Further, patients who are prescribed drugs on therapeutic grounds usually will be aware of the drugs' names only on receipt, for instance, of the packaging and package inserts, but the names of the manufacturing companies will be immaterial. Patients receiving drugs by injection will know their purposes but not necessarily their names. Physicians are not required to name manufacturers of the drugs they recommend. In contrast, however, a subject who is asked to accommodate a physical intervention or compromise of medical-file confidentiality for the sake of a post-marketing surveillance study or of an investigation of an adverse drug reaction is entitled to know not only what is being requested that departs from therapy, but also on whose immediate behalf that accommodation is requested. Subjects willing to assist one manufacturer or type of manufacturer may be less accommodating of another, even on irrational grounds. Prospective subjects must be informed about why they as opposed to others are being approached, who will have access to any information they may provide and, for instance, the reasonably foreseeable consequences for them and their future care of participation in the study.

In some countries, such as the United States of America, legislation or subordinate regulations ritualize the processes of making disclosures and receiving consent for purposes of research. Surveillance studies will have to conform to such legislation or regulations, although non-conformity may expose investigators to administrative sanctions or legal accountability such as for breaches of contract or institutional employment, but not necessarily give legal claims to subjects recruited to studies by irregular processes.

3. Classification of surveillance studies — clinical and epidemiological studies

It has been seen that ethical codes for research may achieve legal enforceability through their express or implied incorporation in private contracts, such as of institutional employment or between product manufacturers and investigators they engage to conduct surveillance studies. Ethical codes may also be material when public authorities or governments agree to permit studies, or require that studies be undertaken, for instance as a condition of continued approval of a product for use. The expectation is that such studies will reflect ethical considerations. Accordingly, the classification of a surveillance study as

either a clinical study or an epidemiological study, bound by the ethical principles relevant to clinical studies[4] or to epidemiological studies respectively,[5] is of legal as well as ethical significance.

It has also been seen that purely statistical surveillance studies, carried out by patients' physicians, that employ data gathered or presented anonymously and that cannot be linked back to identifiable individual persons, such as data aggregated at their source and applied in cohort studies, will not be classified as human-subject research that requires individual consent from the persons whose data are used.

Nevertheless, it cannot be concluded that, because these studies do not have to conform to guidelines on clinical research, no consent is required to conduct them. When epidemiological studies are conducted that involve or affect identifiable populations or communities at large, some input from and approval of members of such populations or communities may be an ethical requirement that will receive legal recognition.

It is only relatively recently that collectivities of people have been acknowledged to have interests in preservation of their confidentiality and dignity, and in control of interventions that may affect their resources, capacity to pursue their self-determined priorities, and their members' social and individual health.[6] This has long been implicit in the legal origin of public health legislation, which arose not in the health but in the policing powers of states. Like those who render more obvious police services, public health officials possess legal powers to oblige the public to provide information, to detain individuals on suspicion and hold them in quarantine pending investigation, to compel individuals to make disclosures of their contacts and for officers to trace contacts, and to oblige those found dangerous to the public to undergo treatment or restraint.

Because public health powers have historically been founded on the authority and responsibility of governments to protect populations, the aspect of consent to its exercise has been obscured. However, following "steps towards the democratization or laicization of the field" of bioethics in the last two decades,[7] recognition has grown that collectivities may assert their interests independently of government, seek consultation on studies likely to affect them, and claim powers to approve or disapprove such studies. Members of groups concerned with HIV infection and AIDS have recently been most visible in several countries in advancing this understanding.

Consent to epidemiological studies that involve individuals' identifiable data should in principle include that of each individual concerned, consistent with principles governing clinical interventions. There may be good reasons, however, for this requirement to be waived by an authorized, independent ethical review agency, such as impossibility or excessive cost when failure to conduct the study would prejudice public health, or when prospective benefits of the

knowledge gained convincingly outweigh irreducible loss of confidentiality. Too much should not be made of the historic principle *salus populi suprema lex* (the health of the people is the highest law), but when risk to individuals is minimal, such as marginal reduction in confidentiality of medical data of no special sensitivity, and the risk to many more is considerably greater if a surveillance study is not conducted, the public interest may justify conduct of the study without individual consent. Approval should be subjected to stringent safeguards of confidential information in the hands of investigators.

Endorsement of a study may be sought at a public or political level through due prior publicity and notification. This is illustrated when drug licensing authorities approve prescription of a drug subject to subsequent surveillance studies of outcomes and reactions. It is recognised that individual consent of patients may not always be practically obtainable. Further, it is unlikely that a manufacturer required to conduct such a study could decline on the ground of lack of consent to access to data by individual patients. A governmental sanction against the manufacturer of withdrawal of approval to marketing of the drug would be dysfunctional to the public interest when the drug had been conditionally approved earlier because of its therapeutic function.

When drug manufacturers initiate surveillance studies without governmental request, it may be more difficult for them and their investigators to claim legal authority to gain access to individuals' identifiable medical information without the individuals' prior, adequately informed consent. Legal distinctions are recognized, however, between nonconsensual access to information that is considered not to constitute a breach of confidentiality, breaches of confidentiality that are justifiable, and breaches that are not justifiable but that are excusable. This last category is legally wrong in principle, but such breaches warrant no punishment or compensation because they serve a tolerable conscientious purpose. At worst, surveillance studies that are bona fide and competent attempts to identify, for instance, contraindications to use of an approved drug may come in this category. In contrast, a purposed "study" of which the primary goal is to promote a practice of prescription of a drug among physicians by offering them free introductory supplies in exchange for outcome information will not. In any event, some attempt should be made to obtain study approval on behalf of any identifiable affected community.

When a community exists independently of a study, with an authentic social structure and group self-awareness, cohesive interaction and discernible leadership, contact may be made with the group at the planning stage of the study. Its views can be sought through individuals able to represent or speak for the group, and its collective approval can be gained. Beyond inhabitants of an area, common sufferers from a disorder, for instance, or family members of sufferers,

may form themselves into a society or group of this nature. When a group is a purely statistical construct, however, defined only by the admission criteria of a scientific research protocol, whose members have no relationship to one another and do not identify themselves with one another, this level of group representation and participation is impossible. Individuals can be engaged in relevant discussions, but their approval carries no more than individual weight.

Even the former groups, involved through credible representatives, cannot give legally effective consent to invasions of individual group members' bodily integrity or confidentiality. Their significance is that they may facilitate surveillance-study investigators in discharging their legal duties to observe ethical guidelines on epidemiological studies by demonstrating respect for collectivities of peoples and for collectivities' ethical rights to autonomy. Like other ethical rights, of course, these are not necessarily absolute, but have to be weighed against other ethical values, such as beneficence, non-maleficence and both distributive and compensatory justice.

4. Legal standards of care and negligent non-disclosure

"Informed consent" is a legal term of art relevant to medical decision-making; it possesses different meanings, applications and implications among different jurisdictions.[8] Those that deny that they apply the doctrine in a form familiar in another jurisdiction have a variant of it in their own, since no jurisdiction denies the principle that individuals of adult years and intellectual competence enjoy bodily and personal self-determination, subject to specific legal limits on such grounds as emergency, morality, public health and public order. Laws that limit self-determination tend to restrain positive actions that individuals may wish to undertake for themselves, but leave considerable scope for individuals to restrain bodily or other interventions against themselves that others may wish to impose. The legal condition of any such interventions is the prior consent to those proposed to be subject to them, and the consent must be adequately informed of the nature and quality of the proposed interventions.

Interventions that lack consent or that depart from or exceed any consent given will be legal wrongs that merit punishment and compensation. In addition, however, many legal systems recognize that the duty to give proposed subjects of interventions adequate information for their decision-making is part of a general duty of care, violation of which constitutes legal negligence. Breach of the duty of care consists in failure to act according to the legally determined standard of care. The negligent breach of duty may become legally actionable when it causes damage. Negligent disclosure causes damage if it results in decisions that lead to harm when, with appropriate disclosure, informed individuals would have made different decisions.

For instance, administration of a drug will usually bear an irreducible minimum risk of an adverse reaction that no amount of care can prevent. If a patient gives adequately informed consent to take the drug and suffers an adverse outcome, it will be very difficult for the patient to show that negligence was the cause. If, however, the patient was negligently not informed about the drug or, for instance, about alternatives to its use, and therefore consented to take it and can show that, with proper information, a different decision would have been made, the adverse outcome will be held in law to have been caused by the negligence. This is so even if the patient was adequately aware of the risk of the actual harm that resulted, and the risk was inherent in the product and not a result of faulty design, manufacture, prescription or, for instance, administration. Causation in law is the result not of a fault in the drug, but of the negligence that led the patient to the decision to take it.

The standard of required medical disclosure is set by the law, but not in the abstract. Courts will not usually set unrealistic standards. They will be guided, although not governed, by disclosure practices within the medical profession and the pharmaceutical industry, in their domestic and other relevant markets, judges' perceptions of what patients need to know to make decisions that protect their interests, and in particular by what information is actually available and is feasible and necessary to acquire. The significance of post-marketing surveillance studies is that they demonstrate what information of outcomes of drug use is considered feasible and necessary to obtain, and what information actually exists.

There is no legal duty to provide patients with information that does not exist or that is not reasonably suspected to be true. Patients must be informed, however, of such facts as that a drug, though approved for use, has not yet been subjected to long-term follow-up studies of its safety and efficacy. It may not be long before courts, particularly in developed countries, require women — of reproductive age, for instance — to be informed that drugs or dosages of drugs proposed for them have not been tested on women if they have not been, and geriatric patients to be similarly informed if drugs or proposed dosages have not been proven safe and effective for elderly patients.

Courts will attend to post-marketing surveillance drug-studies that have been conducted, required or recommended in order to determine standards of disclosure of information to which prospective users of drugs are legally entitled, and to identify which non-disclosures are negligent. Single-case adverse reactions associated with drugs that have been in widespread use will not have to be disclosed unless further studies or suspicions have linked the reactions to the drugs. When a contraindication is responsibly identified, however, drug companies will be expected to warn physicians rapidly, and they in turn will be

expected to warn patients for whose conditions they propose to recommend or to continue to recommend such drugs.

Modern electronic techniques of rapid collection and analysis of massive volumes of data will improve possible means of surveillance. Courts will not set standards of performance by requiring nothing less than the best that science or the pharmaceutical industry can achieve, but will be conscious that standards are improving and that companies fall behind in vigilance and proficiency not only at their competitive peril but at their peril of legal liability too. Standards will be influenced not necessarily by the performance of a defendant company but by expert testimony of standards conscientiously considered appropriate in the industry for a fair balance between consumer protection and competitive economy. Beyond setting standards of surveillance that companies should undertake, courts will consider accessible information that has been produced by other manufacturers, at home and relevantly abroad, and by international organizations and academic contributors to the relevant literature.

Accordingly, manufacturers of prescription drugs will be expected to conduct surveillance studies of their own and make material findings available to physicians, pharmacists and other relevant health professions. They will also be expected to know and apply findings that are reasonably available to them from other manufacturers' studies, to participate in national, regional and international means of exchange of information and to monitor the evolving relevant literature. In particular, a subsidiary of a parent company will be hard put in court to explain that it was unaware of information available to a twin subsidiary or to the parent company's head office but was not negligent. It is a legal principle of criminal liability that information available to officers of a company is imputable to the company itself, which is deemed to know what each of them knows, and courts may be persuaded to adapt the principle to product liability and duties of care to disclose information.

As electronic-data-processing techniques advance and become economically accessible, and as rapid transfer of information becomes increasingly possible, courts will expect them to be used for the protection of patients. Manufacturers that maintain contemporary efficiency in conduct and awareness of surveillance studies, and that equip physicians and others with the information to use their products to maximum benefit and minimum harm, will satisfy legal standards of care that bind them in disclosures to which prospective consumers are entitled.

End-notes

1. Phases of drug development studies in human subjects are described in *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, Council for International Organizations of Medical Sciences, 1993, Annex II, pp.51-2.

2. See Robert J. Levine, "Informed Consent in Research and Practice: Similarities and Differences" 143 *Arch. Intern. Med.* (1983), pp. 1229-1231.
3. See Dieter Giesen, *International Medical Malpractice Law* (Dordrecht: Martinus Nijhoff, 1988) pp. 376-392.
4. See the CIOMS Guidelines, note 1 above.
5. See *International Guidelines for Ethical Review of Epidemiological Studies,* Council for International Organizations of Medical Sciences, 1991.
6. See Z. Bankowski, J.H. Bryant and J.M. Last,(eds) *Ethics and Epidemiology: International Guidelines* (Geneva: CIOMS, 1991).
7. John H. Bryant in Z. Bankowski, J.H. Bryant and J.M. Last, *ibid.* at p.9
8. See generally, Dieter Giesen, note 3 above, Part II Disclosure Malpractice, pp. 252-369.

THE PARADOX OF WIDELY AVAILABLE AND RESTRICTED INFORMATION

Judith K. Jones*

We have a paradox of information. We have both too much information, as I implied in my remarks yesterday, and access to information through a number of different channels. They are widely available, so to a certain extent the notion that we can protect information — that is, as regulators and others — may be a fallacy. it is widely available to patients. We should recognize that. Even scientific information is widely available. Computer networks such as Internet are now becoming the new channels of information, which go around all the formal gatekeepers of information. So we are in an era of open information, and this is probably why we are breaking down boundaries throughout the world in the political arena, and I would say there is definitely an analogy here, as I will mention in a minute.

The other part of the paradox is that there is closed information. There is growing interest in restricting access to information. This is a major threat to our understanding of what is happening. There is a great need to foment responsible use of information. The charge is that we have to have a system in which we can have both proper management of good information and responsible use of the information, with protection of privacy, somewhat as discussed by Professor Dickens. How do we do this? I think we have to think about a somewhat different design of where we are. This is apropos of the time, certainly in the current political environment. It is very clear from the participants here that we live in a global village. We are redefining, and we need to redefine, the community in which we live.

One of the ways — when I came to the FDA and looking at the adverse reaction system — we approached this was by looking at it from a systems standpoint. We are very much in the environment of evolutionary systems. A systems approach is to look at input, process and output and ideally at what one's goals are. Obviously our goals are to have informed patients who can manage their drug therapy and, more largely, their health. Everyone would agree with that. How do we do it? I think we do have to redefine the community, as is being done. Because of the dissemination of information the hierarchies of all of our relationships are flattening, for everyone has access to the information. The hierarchy based on information is no longer there. We have also seen examples, and very successful ones, of the decentralization of that hierarchy, in the French and Swedish adverse-drug-reaction systems, but such decentralization through information and exchange of information probably needs to extend all the way down to the

* The Degge Group Ltd., Drug Safety Research and Information, Arlington, Virginia, USA

physician and the patient exchanging that information. We need in this redefined community to redefine some roles and responsibilities, and the important thing is not to leave out any of the participants.

There are some participants, I think even in this discussion, who have been left out to a certain extent or have left themselves out. One group has to do with academia and their responsibility in recognizing the rest of this community, in recognizing the output. If medical schools had to be as responsible as manufacturers for their products they would fail terribly in their physicians' use of drugs. So we have to involve the academicians and call upon their level of responsibility. We also in this coming age of managed care, particularly in the United States, and perhaps in other areas, have to call upon the responsibility of those who make decisions about use of drugs and are administratively responsible for doing so. We have to involve those people and we have to co-opt and involve all participants in this process, which is a much more flattened process than it has been.

I would leave you with an analogy that perhaps is not appropriate but I think does represent a shift of responsibility. If you look at the transportation systems in most developed countries I would say that in the past, and decreasingly perhaps the present, they have been operating a little like the air transportation system, which is quite paternalistic. Our therapeutic system is to a certain extent paternalistic — both the regulators to the manufacturers and the physicians to the patients. We are seeing that diffuse, and the regulators and manufacturers, as evidenced by the CIOMS effort, are talking around the same table and sharing in consensual decisions. The future vision may be analogous to surface transportation, particularly cars, because everyone who drives a car takes a lot of responsibility for the use of that product. It does have a policing action analogous to the public health issue that Professor Dickens mentioned, and perhaps there is an analogy there. It cannot be carried too far but I would say there does need to be a restructuring of responsibility and involvement of everyone in the community.

ACCESS TO PATIENT INFORMATION

Charles Medawar*

Access to patient information is the stuff of whole conferences and it is going to be very difficult to deal with it in the very limited time available this afternoon. I shall necessarily make sweeping generalizations. Inevitably I shall confine myself to matters relating to the overall context of this meeting — that is to say, access to information in the context of adverse-drug-reaction monitoring. I shall emphasize also, I hope, where I want to be in future rather than dwelling on, in some ways, the rather sad past.

I want to pick up where I left off yesterday by restating that it is clear enough that adverse-drug-reaction monitoring systems must be regarded as an integral part of the drug licensing system. If the original licensing system was the car, the addition of post-marketing surveillance system might be compared by analogy to the introduction of disc brakes; cars should not be driven without them, not these days anyway. However, it is clear that such systems are not without their dangers. I have already mentioned the problem of under-reporting, and perhaps with so much obviously superfluous data flying around it might be better to rely on collecting better-quality information from fewer physicians — when in any case the majority do not report adequately anyway. And that is the kind of solution I would think might be more meaningful to less developed countries, which have of course enormous, almost insuperable, problems with resources. Dangers include also, as I hinted yesterday, the temptation to skimp on pre-marketing approval and a fair example of this was the drug nomifensine. This case has been cited as a classic example of a drug the ill-effects of which were detected through adverse-drug-reaction systems and it was withdrawn in 1986 — but do not forget that the Swedes had never approved it; they decided in 1984 that this drug had an unacceptable incidence of allergic reactions.

There is also a problem with time lag. I am now revealing a secret, by telling you that when the drug regulatory authorities in my country became alarmed about triazolam in 1989 they negotiated with the manufacturers a post-marketing surveillance study, the results of which would not be complete until 1994. Professor Shapiro made a plea, which I can well understand, for no quick fixes — but my plea would be for no slow fixes either. I think the challenge for post-marketing surveillance is not to refine the technologies in order to look for even smaller needles in even larger haystacks: to my mind the challenge for the future is to develop faster and more reliable systems, and then to overcome the enormous problems of communicating the hard, often

* Social Audit Ltd., Box 111, London NW1 8XG, England

excellent, data that derive from well-planned studies. At present, prescribers often do not use that information at all.

I was pleased, but also perplexed, to hear with Judith Jones had to say. She kept on saying "we" and I think she was talking about the United States, for she was describing a situation which in some respects is totally unfamiliar to me. About 25 years ago (give or take probably 10) I saw a New Yorker cartoon of which I was reminded when thinking about what I was going to say today. In the bottom right corner was a missionary, in a jungle clearing, and the missionary was pointing up to the sky to an aeroplane. There were two natives leaning on their spears looking slightly perplexed, one talking to the other saying: "Holy Father says that is a great white bird but it looks to me like an extended-bodied DC-3!" For "missionary" read "medical establishment".

The challenge for the future as I see it is for the medical establishment in general, and for epidemiologists and clinical pharmacologists in particular, to develop much greater responsiveness, an acceptance of the notion of accountability and more of the disciplines of democracy. What medicine needs is to pass some test of public acceptance and that has got to be an informed acceptance. There is a great deal more to explain, there is a great deal more for the public to understand. Medicine needs a greater degree of public trust; this is now lacking and arguably is fading.

Professor Asscher mentioned at the beginning of this conference the absolute inevitability of another drug disaster, and having listened to Professor Sjöqvist you have a pretty good idea how it is going to happen and also the time-scale. But what is the public going to think when they are told yet again, with bland reassurances: "but of course no drug is safe, all drugs have adverse drug reactions"? It really is not good enough. The secrecy that still blights medicine today seems to me to be a hangover of the clinical freedom that blighted medicine certainly in my adult lifetime and, in some parts of the world, continues to do so today. That secrecy is also the stuff of political advantage; it is also the stuff of commercial gain.

Now commercial gain within limits is acceptable and desirable; beyond those limits it is totally unacceptable; in medicine, I am afraid, there is a good deal of transgression and it leads in my view to an abuse of public trust. The traditional reason given for secrecy in medicine, and thank God I have not heard it said at this conference — for I think I would have screamed — is that the public would be alarmed, would be confused, if they were to get too much information. But evidence on this is slight. I did a MEDLINE search before I came here, conjoining the words "public" and "alarm": I got 11 citations, not one of which had anything to do with drugs. What patients are you talking about when you talk about patients being alarmed?

The problem with secrecy is that it prevents the development of an infrastructure of understanding and trust — and this is to me so perplexing when medicine in so many ways is so great today. It is as perplexing for me to hear there must be secrecy because the public cannot understand, just as it would be perplexing for many of you to hear me urge secrecy over the benefits of medicine on the grounds that many physicians might get carried away. It's clearly absolutely absurd. The reason for openness is best explained in the excellent WHO report, *New Approaches on Health Education and Primary Health Care,* 10 years ago (WHO Technical Report Series 690, 1983):

> "...science and technology can contribute to health standards *only* if the people themselves become full partners of the health care providers in safeguarding and promoting health... People have not only the *right* to participate individually and collectively in the planning and implementation of health care programmes, but also a *duty* to do so."

It was followed up with a statement which makes a fundamental point about the need for openness:

> "Openness and effective communication are basic to the success of a drug policy ... Public participation is crucial to the attainment of health for all by the year 2000; it is needed to provide checks and balances in decisions relating to the allocation of resources and acceptability of drug risks."

We are not talking here about patients' rights; we are talking about a discipline that medicine in particular and science in general needs. It is discipline that it must have if it is to work as effectively as it might.

Obviously there is a need to protect patients from risk, and that risk will be reduced with better understanding and with greater intelligent compliance. Intelligent compliance may sometimes include non-compliance, in my view.

There is another aspect to openness and the need for it, and that is simply consumer rights — and I distinguish here between "patients' rights" and "consumer rights" because patients increasingly claim rights to have some say in the organization of services for which they pay and which in political and in many other ways may deeply affect the way they lead their lives. In 25 years time I think I can see, but I hope it will come sooner than that, a yellow-card system which is in fact consumer-led, perhaps as Professor D'Arcy would like, with the pharmacist holding the hand of the consumer — so it is the consumer who may have suffered the adverse reaction who prompts the doctor to do what so many doctors do not do nowadays. I believe that one of the reaons for secrecy, one that has not been touched on so far, is not to disguise evidence that is held in files — deep damaging secrets, smoking guns — but to hide evidence of how much is not known. To use Stephen Evans' lovely phrase, the problem is that greater disclosure would make uncertainty explicit. But it would be more scientific to do so, it would be

more humane to do so, it would be more intelligent to do so, and it is a better way of making progress to do so. It has to be. It is the first responsibility of all professions and all professionals not to exceed their limitations — which is always a danger if you do not know what your limitations are.

Let me summarize what I have to say by quoting from the resolution of Health Action International (Europe) in November 1992 — a statement which explains why secrecy is becoming, deeply, politically incorrect:

> "Secrecy in medicine is pervasive, largely unnecessary, and an obstacle to health. Lack of information limits freedom of choice, diminishes science and inhibits constructive participation. Secrecy also tends to hide evidence of inefficiency, incompetence and inappropriate behaviour, and therefore tends to reduce levels of public confidence and trust."

Dr. Lumpkin made the point that the patient is clearly the most important stakeholder, and if there is an important challenge before this conference — and indeed to medicine in general — it is to make that, not lip-service, but much more of a reality in the future. I have felt at times in this conference rather like a statistic and, as you know, statistics don't bleed. I would prefer to have felt at times more like a person and certainly not to have my prospective death compared with that of a drug. The challenge for medicine is very simple: it is simply to explain and justify what it does and thereby to earn public trust. I think that can be achieved in the next 25 years but we really have to make progress at a far faster rate, with far greater determination, than we have done so far. We need much more openness, please, in the next 25 years. It is wonderful medicine.

THE USE OF ANONYMIZED PATIENT DATA

Norman Taylor*

We have all been assuming over the last two days that the data we need will be readily available — sometimes expensive and difficult to obtain but available nevertheless. However, we could imagine a situation in preclinical research in which the animal rights campaign denied toxicologists the laboratory animals they needed. We could also foresee epidemiologists and other workers in the post-marketing field being denied access to the data they required. The issue is no less than the balance to be struck between the needs of society and the rights of the individual. This is a problem which has been troubling philosophers and jurists for the last 3000 years, so we are hardly going to solve it today. But we are left with the problem of an imperfect balance between these competing needs and rights, and particularly the problem of deploying society's resources most effectively. The Chairman invited his discussants to consider his paper on informed consent and research in practice, which deals with the problems of informed consent in research and the problems of informed consent in practice. I want to talk about information issues in research *on* practice. In this area, just as much an important data subject is the doctor, as important as the patient and the patient's response to drug therapy. I want to cover some of the coming problems in access to patient data in observational studies.

Real life means observing the world outside the area of randomized control trials — it includes a concern for miscommunication, misunderstanding and misuse, just as much as data-sheet compliant use. Here I want to identify, for the purposes of data access, a couple of the issues. Retrospective studies pose problems in obtaining patient consent to the use of personal data; patients may be difficult to contact, they may have moved or died, or they may not be competent to give consent. In the use of multipurpose data-bases, such as Dr Jones referred to, in the computerized administration of medicine we have a different problem. It is impossible to know in advance what the nature of the problem to be studied will be and therefore impossible for the patient to give in advance informed consent to the use of information. What are some of the applications of observational research? We have thought about several of them during the last two days — the natural history of disease, particularly some of the issues related to ADR testing, and Dr. Edwards has referred to the use of observational data to set up denominator values. But I would like also to refer to the last three items, which may be somewhat surprising in that they are economic issues. Dr. Antezana has invited us to think about cost-

* IMS International, London, England

benefit analysis of drugs and procedures, and in a world in which the cost of health care is rising these are just as important issues for society as concern about analysis of adverse drug reactions. Therefore many groups have a legitimate interest in anonymized output from observational studies. They are not limited to researchers and clinicians; they include pharmaceutical manufacturers, drug regulators, health planners, health funders — extremely important, patients' organizations, social researchers, the media, and politicians, for policy formation.

Let me change gear here for a moment and say that we all have great sympathy with patients who are caught up in the gears of the media machine. The identities of such patients are obviously to be protected. In this regard we can all agree that there is a need for regulation and data protection. But there is a growing body of regulation which has the capacity to impede the many worthwhile purposes of observational research. I have identified three levels and three processes: *data protection at the national level,* which is designed to protect individual privacy and will be implemented by legislation, and which is fairly benign as far as anonymized data are concerned; *data protection at the supra-national level,* such as is typified by the EC data directive, which is somewhat more intrusive; and *data control,* which is yet more intrusive and malign.

National data protection in the United Kingdom

The Data Protection Act 1984 in the UK and the guidelines issued by the General Medical Services Committee of the British Medical Association permit anonymized use of data: "data when anonymized are no longer personal and their use is not a disclosure". Doctors are given the sensible advice that they should explain to patients the practices involved in research and that it is wise to reassure patients that they cannot be identified by use of their anonymized data.

The European Commission Directive on Data Protection

This Directive was presented to the European Parliament in 1992 and amended as a result of that presentation, and is now expected to be adopted by the member states without substantial change. Its purpose is relatively benign but it is wide-ranging and in some aspects imprecise in its operation. Interpretation can be provided by Commission staff, but of course the interpretation is not binding and we will have to wait the arrival of cases in the courts for the final resolution of imperfections. The start-point is essentially unpromising and the freedoms which we need have to be clawed back in the sub-paragraphs. First, the Directive covers personal data, and the sub-para starts off by saying "processing personal data requires written patient consent". Written patient consent across 350 million people in the European

Community presents some logistic problems. Data could be depersonalized; obviously this is what we would like but the Directive indicates that depersonalization itself is data-processing and therefore forbidden, and that is the catch-22. It does go on to say that processing may be carried out where there is manifestly no infringement of the patient's privacy or freedom. At least one department of health in the European Community has taken legal advice on this point and understands that it means still that one can use it only for the care of the patient and for the immediate administrative purposes of the health-care provider. According to the Directive, "personal data" means any information related to an identifiable person — one who can be identified directly or indirectly by one or more factors; this raises the problem of what I call the red-headed dwarf, the case where indirect identification can be achieved by successive subdivision of the data and the patient finally identified. There is no indication of the level of subdivision which is considered unacceptable. A previous draft had a guideline that said where this could only be done at unreasonable cost. That has been dropped from the present text and now the case remains to be tested in the courts.

Data control

I use the UK National Health Service (NHS) as an example of data control. There is a general situation here, where the NHS is a data provider. The same case may arise in regard to health maintenance organizations, insurance companies, medical cooperatives, and anyone who employs doctors to provide medical services. In the NHS the legal view is that general practitioners owe a duty of confidence not only to the patient but also to the NHS itself. The NHS records are held by NHS doctors on behalf of the NHS rather than for their own or their patients' purposes. Doctors who provide information to parties outside the NHS are in breach of duty to the NHS. Anonymization does not justify disclosure of data, and anonymized disclosure for commercial purposes is a breach of duty of confidentiality owed to the NHS. These are all extremely tough and restrictive provisions, which if implemented after consultation will cut a swathe through the use of data for many significant worthwhile purposes. In particular, with economic pressures driving to fragment health care provision, we must be concerned about other health-care providers and funders taking a similar view to that of the NHS. I believe this threat to data freedom is likely to grow, and that all those who believe that the balance on data availability threatens to move against the public interest should make their voices heard whenever the case presents in their environment. There is the risk of a shadow of data regulation falling across health-care research. The price of research freedom is eternal vigilance.

DRUG SAFETY MEASURES AND PUBLIC RELEASE OF DRUG-PRODUCT INFORMATION IN JAPAN

Osamu Doi*

Introduction

It is said that the usefulness of a drug product should be judged on the basis of the balance between its risks and benefits. For the maximum efficacy of drug therapy, the efficacy of drugs should be maximized and their adverse reactions minimized. To do so medical institutions must be supplied with highly effective and safe drugs, and at the same time drugs must be appropriately employed in medical practice on the basis of sufficient information. In Japan, to assure the efficacy and safety of drugs from the research and developmental stage through the stage of actual use and application, the Pharmaceutical Affairs Law enforces a number of regulations.

Dissemination of drug information to medical institutions, patients and the general public

Information on the efficacy and safety of a drug is obtained during each of the various stages of its development and life, from the phase of research and development through the stage of the examination of the new drug for approval, re-examination, re-evaluation and post-marketing surveillance. To promote the appropriate use of drugs in Japan, this information is made available to the greatest extent possible to medical experts, and the Ministry of Health and Welfare (MHW) is striving to make this information available to patients and general consumers.

Public release of information at stage of approval

It is required that the principal contents of the application for approval of the new drug be published in scientific journals, and efforts are being made to achieve public release and transparency of drug information.

In addition, from 1994, with regard to newly approved drugs, the MHW will prepare a *Summary Basis of Approval* of the information on their efficacy and safety obtained at the time of the examination for approval, and will quickly distribute it to medical institutions. As this information will be accessible to both medical institutions and general consumers, it is expected to improve the transparency of the system for examination and approval of new drugs as well as promote the appropriate use of drugs in Japan.

* Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Japan

The *Summary Basis of Approval* is expected to include the following items:

Name of the product, name of the manufacturer
Name and content of active ingredient(s)
Dosage forms, route of administration, dosage
Indications or effects
Precautions for use
Information on manufacturing process
Data from the results of non-clinical studies in animals (toxicity, pharmacological action, absorption, distribution, metabolism and excretion)
Data from the results of clinical studies (efficacy, safety)
Processes and conclusions from discussions of the Central Pharmaceutical Affairs Council

Public release of information at stage of re-examination

In Japan the Pharmaceutical Affairs Law stipulates that the manufacturer is responsible for compiling data on the clinical cases of actual use of a drug in the medical institutions for a period of, in principle, six years after approval of a new drug, and submit an annual report of those data to the MHW. Moreover, after six years, the MHW re-examines the efficacy, safety and quality of the new drug on the basis of the data received during the re-examination period.

During the re-examination periods, the MHW carries out an evaluation of the adverse-reaction reports submitted to it each year. In addition to devising safety measures such as revision of *Warnings and Precautions for Use*, the MHW prepares reports entitled *Information on Adverse Reactions* every two months, and distributes them to the medical institutions. They are released also to the public.

Moreover, at present, only the results of the re-examination carried out six years after approval of a new drug are being publicly released. However, from 1994 the information regarding the examination for approval of a new drug will be released in the form of a *Summary Basis of Approval* and the MHW is conducting studies to determine whether, as the next step, similar public release of information about the re-examination — in the form of a *Summary Basis of Re-examination* — in the near future would result in the more appropriate use of drugs.

Public release of information at stage of re-evaluation

The Pharmaceutical Affairs Law stipulates that all prescription drugs must be re-evaluated for efficacy and safety, in principle, every five years. Drugs are selected for this re-evaluation by screening on the basis of information published in Japan and overseas, adverse-reaction information, and materials submitted by the pharmaceutical industry

relating to their efficacy and safety. Only a summary of the re-evaluation and its results is being publicly released.

At present, the MHW is not planning to compile a summary basis of re-evaluation for public release, because (1) the materials used for the re-evaluation are not systematically prepared, and (2) most of the materials for the re-evaluation are based on papers already published in Japan or in other countries.

Public release of information on adverse drug reactions

The Pharmaceutical Affairs Law stipulates that pharmaceutical manufacturers compile and report to the MHW information from the medical institutions on the efficacy and safety of their drug products. The MHW thus — via the pharmaceutical manufacturers — compiles information on adverse drug reactions.

Moreover, the MHW has established an adverse-drug-reaction monitoring system through the cooperation of medical institutions and pharmacies, which transmit information on adverse drug reactions direct to the Ministry. This information is then evaluated from the medical and pharmacological viewpoints in the Ministry's Central Affairs Council. Safety measures are devised, such as revision of *Warnings and Precautions for Use*, distribution of *Doctor Letters*, and revision of *Dosage and Administration* and of *Indications*.

In particular, with regard to the revision of *Warnings and Precautions for Use*, including the *Doctor Letters*, the manufacturer must inform medical institutions, etc. throughout Japan of the nature of those changes within 30 days of making them. In addition, the Federation of Pharmaceutical Manufacturers Association of Japan also prepares a monthly leaflet which thoroughly summarizes the information and mails it to approximately 200 000 medical institutions and pharmacies.

Moreover, the MHW prepares the most important information in the form of *Information on Adverse Reactions* and distributes it to the main medical institutions throughout Japan every two months. Any interested person can access this information by means of a nation-wide facsimile network, and it is also reported in medical and pharmacological journals. In addition, English translations are prepared and distributed to countries participating in the WHO International Drug Monitoring Programme.

Problems to be solved regarding provision of information to patients and the general public

From the standpoint of patients and general consumers, access to information about drugs is still considered inadequate, for the following reasons:

(1) Progress has been slow in separating dispensing of drugs from medical practice; physicians commonly hand drugs directly to patients, with no explanation of the nature of the drugs.
(2) The concept of informed consent is still not well understood or applied by medical-care practitioners and therefore they often do not explain to patients the nature of the drug, its expected efficacy, or its possible adverse reactions.
(3) Because the medical experts are very busy they often do not have the time to give patients adequate directions on how to take the drugs or to respond adequately to patients' questions.
(4) The system in Japan's hospitals, etc., does not easily permit patients or the public to receive consultation about drug products.

The MHW believes that, for the appropriate use of drugs, patients must be able to obtain adequate information about drugs and then to take them on the basis of a good understanding of their nature and appropriate use. Accordingly, to improve the access of patients and the public to drug information, the following measures are being implemented from 1994.

(1) The MHW will prepare a data-base including as much information as possible about drugs, including adverse reactions, and will create a nation-wide drug-information network that will be accessible to medical institutions as well as to patients and the public.
(2) The MHW will, in cooperation with the Japan Pharmaceutical Association, establish a drug emergency-call service nation-wide so that patients and the public can easily receive consultations about drug products.
(3) So that medical experts can accurately instruct patients on how to take drugs, the MHW will prepare for patients and others a drug-ingestion instruction manual for each active ingredient.
(4) To make the best use of the professional skills of physicians and pharmacists, and to inform patients of the contents of prescriptions and instruct them thoroughly about taking a drug, the MHW will continue its effort to separate the dispensing of drugs from medical practice.

The MHW is committed to continuous cooperation with drug manufacturers, medical experts, patients and the general public to maximize the benefits of drugs to patients, and, since improved health care is a goal that transcends national borders, to further increase cooperation with other countries through such international organizations as WHO and CIOMS.

THE FRENCH INFORMATION PROGRAMME

René-Jean Royer*

"Increasingly patients are seeking and getting more information about the medications they receive. Concern about proper use and controlling side-effects is evident... But experience suggests that only a small portion of patients receive and comprehend the information that is required to make good decisions about drug therapy and drug use..."[1].

The mass media are the primary providers of background information on which potential patients form their beliefs about drugs. Prescribers are the primary contact for specific information. In France, without neglecting the drug consumers, we bring our efforts to bear on prescribers. Data-sheets, the *Dictionnaire Vidal* (similar to *PDR, Rote Buch, Compendium suisse*, etc.) are the controlled sources of information for prescribers. Some academic or scientific books are available. Training at a medical school is essential.

Two particular features are the provision of information by regional centres, and the training of medical representatives.

1. Information provided by the regional centres

The telephone answering service. The French pharmacovigilance network links 30 regional centres dispersed throughout the country. They have the duty to collect and analyse ADR reports but also to spread information about drugs.[2]

The most frequent type of information service is telephone answering. Physicians often telephone for information about a suspected case of ADR; more and more, they call preventively, to avoid ADR. The answers to their questions are provided by standard textbooks (*Dictionnaire Vidal*, Martindale, Meyler's side-effects of drugs, Drugs, X Reactions, etc.) These are complemented by reports of side-effects — recently published or not — compiled in the above volumes. Finally, the national data bank and the WHO data can help in giving answers on unpublished side-effects. In some specialized fields such as hepatology, pancreatic diseases, or haematology, we use ADRs national data-bank such as Hepatox, Pancreatox and Hematox.

The answers consist of pharmacological advice in respect of a patient (interactions, teratology, help in diagnosis, etc); general information about a drug or family of drugs; and literature references.

In 1992 the number of questions asked of the regional centres was about 25,000. They are more numerous than ADR reports, though some of the subjects of questions are notified later. The telephone call is systematically used to remind the health professionals they have to report. A report form is sent with a systematic mail reply.

* Commission nationale de Pharmacovigilance, Ministère de la Santé, Paris, France.

Other ways of disseminating information. Members of the team participate in postgraduate or continuing medical education. Some centres publish a local information bulletin on recent advances and matters of general interest in ADR management. It is sent to physicians in hospitals and to private practitioners who wish to receive it. The Association of Regional Centres organizes an annual national convention on ADRs, generally with selected themes, and the major lectures are published in *Therapie*. The Association has contributed to the foundation of the European Society of Pharmacovigilance. The centres do experimental, clinical or epidemiological research into the various aspects of ADRs. More than 500 publications have been published in national and international journals.

The educational activity of the pharmacovigilance centres is often bound to the training in clinical pharmacology of physicians, nurses, dentists, pharmacists, and graduate and post-graduate students.

2. The training of medical representatives

In France the pharmaceutical industry employs medical representatives to visit prescribers to inform them about brand-name products. For some time the aim was only to persuade doctors to prescribe a brand-named drug. Now more information is given but it is not sufficiently objective, and under the pressure of health authorities, consumers, academics, doctors, and pharmacists, a collective agreement has been reached between the professional bodies and the Pharmaceutical Industry Federation.

The terms and conditions of the training of medical representatives have been defined. A trade committee has been charged with approving agreements with the teaching partners and keeping the system under supervision. The teaching partners can be universities, medical schools or private teaching groups. Training consists of 250 to 500 hours of academic courses, working groups and professional exercises, including basic practical training.

Only fully qualified persons may work as medical representatives. A partnership between five universities and five pharmaceutical laboratories, called *Partenariat Emeraude,* has been created to help fully qualified people find employment. Others are expected.

References

1. McGallum, D.B., and Yenney S. *Communicating the benefits and risks of prescription drugs* 1988; 1 vol.: 58 pp. Institute for health policies analysis, Georgetown University Medical Center.
2. Lagier G. and Royer R.J. Information to the physician: Role of French regional pharmacovigilance centres. *Drug Information Journal* 1990; **24**: 203-206.

CLOSING OF THE CONFERENCE

John H. Bryant*

This conference, I believe, has provided a systematic coverage of the various aspects of drug surveillance. But it had other dimensions, which rose largely out of the unusual diversity of the subject matter and the participants. It was not a monodisciplinary conference, and this brought even some discomfort, but it also brought a richness — in the exchange of ideas and experience, and the participation of people from different cultures, backgrounds, and disciplines, and with different responsibilities. The field is young and growing; we have had a good exposition of where it has come from, where it is, but also where it is going. This sense of the future is a strong part of what has happened here. We recognize that there is going to be a further strengthening of the administrative systems, of managerial systems of surveillance. The methodologies are advancing even as we sit here. New technologies, particularly the management of large data sets, will play a very important role. These ideas will be included in the education of health personnel. There will be wider participation in the processes involved — doctors, nurses, pharmacists, community people.

One subject we have agreed requires early and intense attention: the needs of developing countries in this field. We know that they have a very limited capacity for surveillance of adverse drug reactions, but this is only a part of their deep weaknesses in the entire field of the availability and safety of drugs. The surveillance of adverse drug reactions should not be considered in isolation from the rest of the context of development. Therefore, we think it would be inadequate, even naive, to suggest that we limit our attention to this field, and I suppose even more so to consider simply transferring the best of this evolving field to developing countries; that would be a mistake. Rather we believe that the best approach would be a consultative process with a prominent role for people from developing countries, as well as for the relevant disciplines, to examine the wider problems of the availability and safety of drugs in the developing world. WHO is doing a great deal already in this regard, and is in a position to take a wider analytical look and on that basis to develop strategies to meet the needs of developing countries.

Such strategies would include surveillance of adverse drug reactions.

The comparable problems of Eastern Europe countries have been mentioned but not discussed. No doubt their needs will be taken into account in the continual international harmonization of drug-safety surveillance.

Now let me ask Dr Vilardell, Immediate-Past President of CIOMS, if he would formally close the conference.

---

* Council for International Organizations of Medical Sciences (CIOMS), Moscow, Vermont, USA

Fancisco Vilardell

Dr Bryant, Dr Antezana, Dr Bankowski, Members of CIOMS, and Distinguished Guests: Dr Bryant has been kind enough to let me close this conference, this, I think, excellent conference, on the monitoring of drug safety. It was kind of him, for he had every right, himself, to close these proceedings.

If you have enjoyed this meeting, you can imagine how much I have enjoyed being at meetings of this sort during six years as President of CIOMS. Dr Bankowski always manages to amass an impressive amount of brain-power at CIOMS conferences. Obviously, this is what results in the very high quality of meetings such as this one.

For this conference, CIOMS had considerable help from WHO's Division of Drug Management and Policies, especially from its Director, Dr John Dunne, who has also contributed substantially to the conduct of the meeting and as a member of the Programme Committee. We are most grateful to him and to Dr Martin ten Ham. I thank all the speakers for their contributions, and I thank particularly the Programme Committee for its efforts in bringing about such an interesting and successful conference. Finally, I am sure you all join me in expressing my appreciation of the efforts of Dr Bankowski and his staff, Mrs Kathryn Chalaby-Amsler and Mrs Christine Dübendorfer, greatly assisted for this conference by Mrs Christine Encrenaz of the Division of Drug Management and Policies.

It has been for me a great privilege to collaborate with CIOMS all these years. You have seen what our new president, Dr Bryant, is able to do, but these are only part of his considerable skills. He has vast experience in medicine and public health, both in the West and in the developing world. CIOMS could not be in better hands. So, with this feeling, and my hope of attending further CIOMS meetings, I declare the conference closed.

LIST OF PARTICIPANTS

ACHENBACH, C. Medizinisch Pharmazeutische Studiengesell e. V. (MPS), Bonn, Germany

AELLIG, W. Clinical Research, Sandoz Pharma Ltd., Basel, Switzerland

AGIKALIN, Y. Directorate of Pharmaceuticals, Ministry of Health and Social Assistance, Ankara, Turkey

ALARY, J.-C. Strengthening of Epidemiological and Statistical Services, World Health Organization, Geneva, Switzerland

ANTEZANA, F.S. Assistant Director-General, World Health Organization, Geneva, Switzerland

ANWAR, N.S. Drug Monitoring Section, Directorate General of Drug and Food Control, Ministry of Health, Jakarta, Indonesia

APPEL, C. ADR Monitoring Division, Health Canada, Ottawa, Ontario, Canada

ARNOLD, B. International Product Safety, Zeneca Pharmaceuticals, Macclesfield, Cheshire, England

ARTHUR, N. National Drugs Advisory Board, Dublin, Ireland

ASSCHER, W. St. George's Hospital Medical School, London, England

AWADZI, K. Onchocerciasis Chemotherapy Research Centre, Hohoe Hospital, Hohoe, Ghana

BANKOWSKI, Z. Council for International Organizations of Medical Sciences (CIOMS), Geneva, Switzerland

BANNENBERG, W. Health Action International-Europe, Amsterdam, Netherlands

BARKER, G.R. ASTRA Pharmaceuticals Ltd., Kings Langley, Herts, England

BELCHIOR, M. Council for International Organizations of Medical Sciences (CIOMS), Rio de Janeiro, Brazil

BENICHOU, C. Direction de la Pharmacovigilance, Roussel Uclaf, Paris, France

BERTRAND, Ph. Pharmacovigilance, Institut de Recherches internationales Servier (I.R.I.S.), Courbevoie, France

BINAME, G. International Association of Law, Ethics and Sciences, Bruxelles, Belgium

BIRIELL, C. Science and Quality Assurance, WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

BLAHOS, J. Czech Medical Association, Prague, Czech Republic

BONDANI, A. Ministry of Health, Mexico, Mexico

BORVENDEG, J. National Institute of Pharmacy, Budapest, Hungary

BOULYJENKOV, V. Hereditary Diseases Programme, World Health Organization, Geneva, Switzerland

BRATTHALL, B. Ministry of Health and Social Affairs, Stockholm, Sweden

BRUMEN, M. Clinical Development Department, KRKA Pharmaceuticals, Ljubljana, Slovenia

BRUPPACHER, R. Pharmacoepidemiology and Central Drug Monitoring, Ciba-Geigy Ltd., Basel, Switzerland

BRYANT, J.H. President, Council for International Organizations of Medical Sciences (CIOMS), Moscow, Vermont, U.S.A.

BUAJORDET, I. Pharmacovigilance Section, The Norwegian Medicines Control Authority, Oslo, Norway

CARMONA, R. Ministry of Health, Lisbon, Portugal

CASA, D. Holy See, Vatican City State

CASTLE, W.M. International Drug Surveillance, Glaxo Inc. Research Institute, Research Triangle Park, N.C., U.S.A.

CAVIN, A.-M. International Committee of the Red Cross, Geneva, Switzerland

CHEN, D. CKW Consulting, Gloucester, Massachusetts, U.S.A.

CHRZANOWSKI, R. Postgraduate University College for Radiology Education, Epalinges, Vaud, Switzerland

CONE, M. Scientific Affairs, International Federation of Pharmaceutical Manufacturers Association (IFPMA), Geneva, Switzerland

CONFORTI, A. Istituto di Farmacologia, Verona, Italy

COOKE, E. Scientific and Regulatory Affairs, E.F.P.I.A., Bruxelles, Belgium

COULTER, D. Centre for Adverse Reactions Monitoring, University of Otago, Dunedin, New Zealand

COURVOISIER, B. Académie suisse des Sciences médicales, Geneva, Switzerland

CROCKETT, E. Wyeth Laboratories — United Kingdom, Maidenhead, Berkshire, England

CZARNECKI, A. Drug Institute, ADR Centre, Warsaw, Poland

D'ARCY, P.F. International Pharmaceutical Federation; Commonwealth Pharmaceutical Association, Belfast, Northern Ireland

DAS GUPTA, P. Drug Control, Ministry of Health, New Delhi, India

DAYEH, K.A. Ministry of Health, Damascus, Syria

DICKENS, B.M. Faculty of Law, University of Toronto, Toronto, Canada

DIECK, G. Pfizer Inc., New York, N.Y., U.S.A.

DOI, O. Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Tokyo, Japan

DULIOS, P. Childhood Immunization Division, Government of Canada, Ottawa, Ontario, Canada

DUNNE, J.F. Drug Management and Policies, World Health Organization, Geneva, Switzerland

EACHENPATI, U. International Medical Sciences Academy (IMSA-New Delhi), Chesterfield, Missouri, U.S.A.

EDWARDS, I.R. WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

ELEK, S. Drug Monitoring Centre, National Institute of Pharmacy, Budapest, Hungary

ELLENBERG, S. Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, Maryland, U.S.A.

EVANS, S. London Hospital Medical College, London, England

FLUSS, S.S. Health Legislation, World Health Organization, Geneva, Switzerland

FORTUNO, V. Association of Pharmaceutical Physicians, Mexico, Mexico

FUCHS, M. Paul-Ehrlich Institute, Langen, Germany

FULOP, L. World Federation of Hemophilia, Geneva, Switzerland

GELLHORN, A. Council for International Organizations of Medical Sciences (CIOMS), Albany, New York, U.S.A.

GIBALA, P. State Institute for the Control of Drugs, Bratislava, Slovak Republic

GOON, E. Division of Development of Human Resources for Health, World Health Organization, Geneva, Switzerland

GORDON, A.J. Pfizer Inc., New York, New York, U.S.A.

GORNICKI, B. Federation of Polish Medical Associations, Warsaw, Poland

GOTTSTEIN, B. World Federation of Parasitologists, Zürich, Switzerland

HACHEN, H.-J. International Medical Society of Paraplegia; International Rehabilitation Medicine Association; World Federation of Spine Surgeons; International College of Angiology, Geneva, Switzerland

HALBACH, H. Prien, Stetten, Germany

HARTIGAN-GO, K. Wolfson Unit of Clinical Pharmacology, University of Newcastle, Newcastle-upon-Tyne, England

HARTMANN, K. Swiss Academy of Medical Sciences, Basel, Switzerland

HASSAR, M. Clinical Pharmacology, Rabat Medical School, Faculty of Medicine and Pharmacy, Rabat, Morocco

HELLING-BORDA, M. Essential Drugs Programme, World Health Organization, Geneva, Switzerland

HERMAN, R. ICI Americas, Pharmaceuticals Group, Wilmington, Delaware, U.S.A.

HODGKIN, C. Health Action International-Europe, Amsterdam, Netherlands

HOFBAUER, E. Federal Ministry of Health, Sports and Consumer Protection, Drug Surveillance, Vienna, Austria

HORST, H.-J. Special Programme for Research and Training in Tropical Diseases, World Health Organization, Geneva, Switzerland

IDANPAAN-HEIKKILA, J.E. Drug Management and Policies, World Health Organization, Geneva, Switzerland

IMBS, J.-L. Commission nationale de Pharmacovigilance, Centre de Pharmacovigilance Alsace, Strasbourg, France

JACKSON, G. Healing Dimensions, Mountain View, California, U.S.A.

JALLON, P. International League against Epilepsy, Geneva, Switzerland

JONES, J.K. The Degge Group Ltd., Drug Safety Research and Information, Arlington,Virginia, U.S.A.

JOURDAN, G. International Medical Forum for Human Rights, Health and Development, Surrey, U.K.

JUILLET, Y. Roussel Uclaf, Paris, France

KATO, Y. Safety Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare, Tokyo, Japan

KIM, Y.-P. Ministry of Health and Social Affairs, Kwachon, Republic of Korea

KONRAD-DALHOFF, I. Bayer AG, Drug Safety, Wuppertal, Germany

KORNFELD, K. Referates Arzneimittelverkehr, Bundesministerium für Gesundheit, Bonn, Germany

KOTHE, F. International Society of Blood Transfusion, Manchester, England

KREMER, G. Corporate Drug Safety, Boehringer Ingelheim GmbH, Ingelheim/Rhein, Germany

KREUTZ, G. Institut für Arzneimittel, Bundesgesundheitsamt, Berlin, Germany

KRISKA, M. Department of Pharmacology, Comenius University, Bratislava, Slovak Republic

KWEDER, S. Division of Epidemiology and Surveillance, Food and Drug Administration, Center for Drugs, Rockville, Maryland, U.S.A.

LANGMAN, M. Birmingham University Medical School, Edgbaston, England

LAPORTE, J.-R. Dept de Farmacologia, Cintat Sanitaria de la Val d'Hebron, Barcelona, Spain

LEOCATA, A. Holy See, Vatican City State

LEPAKHIN, V. Russian State Centre for Drugs, Moscow, Russia

LEVINE, R.J. School of Medicine, Yale University, New Haven, Connecticut, U.S.A.

LIM, A. Drug Administration Division, Singapore

LINDQUIST, M. WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

LOJACONO, G. School of Hygiene and Preventive Medicine, University of Perugia, Perugia, Italy

LOPEZ BRAVO, L. Leprosy Unit, World Health Organization, Geneva, Switzerland

LOWRANCE, W.W. RAD-AR Foundation, Geneva, Switzerland

LUMPKIN, M.M. Office of Drug Evaluation, Center for Drug Evaluation and Research, Food and Drug Administration, Rockville, Maryland, U.S.A.

MACH, E. c/o Council for International Organizations of Medical Sciences, Geneva, Switzerland

MAHMUD. A. National Pharmaceutical Control Bureau, Kuala Lumpur, Malaysia

MALAM da COSTA, E. Essential Drugs Programme, Ministry of Public Health, Bissau, Guinea Bissau

MANN, R.D. Drug Safety Research Unit, Southampton, England

MANSOURIAN, B. Office for Research Promotion and Development, World Health Organization, Geneva, Switzerland

MASSEVA, E. National Drug Institute, Center for Adverse Drug Reactions, Sofia, Bulgaria

MATHIAS, B. Drug Commission of the German Medical Profession, Cologne, Germany

MEDAWAR, C. Social Audit Ltd., London, England

MERRITT-LACHENAL, M. World Federation for Mental Health, Geneva, Switzerland

MOLANDER, S. Uzès, France

MORIN, O. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), Geneva, Switzerland

MOTZEL, C. Medical Women's International Association, Cologne, Germany

MOURA FE, I. Conselho Federal de Medicina, Brasilia, Brazil

MOZINA, M. Adverse Drug Reaction Monitoring Center, Ljubljana, Slovenia

MULLICK, F.G. International Council of Societies of Pathology, Washington, D.C., U.S.A.

NAPKE, E. Formerly Chief, Product Related Diseases Division, HPB, Ottawa, Canada

NUNES, A. C. Instituto Nacional de Farmacia e do Medicamento, Lisbon, Portugal

NUNN, P. Tuberculosis Programme, World Health Organization, Geneva, Switzerland

O'CONNOR, N. Medicines Control Council, Department of National Health, Cape Town, Observatory, South Africa

OGUISSO, T. International Council of Nurses, Geneva, Switzerland

OKSUZ, S. Directorate of Pharmaceuticals, Ministry of Health and Social Assistance, Ankara, Turkey

OLLAGNIER, M. Association française des Centres régionaux de Pharmacovigilance, St. Etienne, France

OLSSON, S. WHO Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

OMBAKA, E. Christian Medical Commission/World Council of Churches, Geneva, Switzerland

PALMA, T. Dangerous Drugs Board, Manila, Philippines

PALVA, E. National Agency for Medicines, Helsinki, Finland

PATWARY, K.M. Division of Epidemiological Surveillance and Health Situation and Trend Assessment, World Health Organization, Geneva, Switzerland

PFEIFFER, M. Drug Safety, Bayer AG, Wuppertal, Germany

PHILLIPS-HOWARD, P.A. Control of Tropical Diseases, World Health Organization, Geneva, Switzerland

PILLAWS, P. National Toxicology Group, University of Otago, Dunedin, New Zealand

PINCOTT, J. Pfizer Central Research, Clinical Safety Evaluation Group, Sandwich, Kent, England

RAM, E. World Vision International, Geneva, Switzerland

RASCHETTI, R. Epidemiological and Biostatistics Laboratory, National Health Institute, Rome, Italy

RAWLINS, M.D. Wolfson Unit of Clinical Pharmacology, Department of Pharmacological Sciences, University of Newcastle, Newcastle-upon-Tyne, England

REINSTEIN, J. World Federation of Proprietary Medicine Manufacturers, London, England

ROBERTS, W. Medical Services, Rhône-Poulenc Rorer, Eastbourne, East Sussex, England

ROISIN, T. Ministère de la Santé publique, Centre belge de Pharmacovigilance, Brussels, Belgium

RONN, O. Kabi Pharmacia AB, Uppsala, Sweden

ROSSINI, L. Department of Pharmacology, University of Ancona, Medical School, Ancona, Italy

ROWSELL, B. Bureau of Pharmaceutical Surveillance, Health Canada, Ottawa, Ontario, Canada

ROYER, R.-J. Commission nationale de Pharmacovigilance, Ministère de la Santé, Paris, France

RUTISHAUSER, W. International Society and Federation of Cardiology, Geneva, Switzerland

RYAN, T. International League of Dermatological Societies, Oxford, England

SAKET, M. Pharmacy Directorate, Ministry of Health, Amman, Jordan

SCHOU, J. University of Copenhagen, Copenhagen, Denmark

de SCOVILLE, A. Académie royale de Médecine de Belgique, Brussels, Belgium

SHAPIRO, S. Slone Epidemiology Unit, Boston University School of Medicine, Brookline, Massachusetts, U.S.A.

SHIBUYA, T. Science Council of Japan, Tokyo, Japan

SHIJA, R. Tadatis, Dar-es-Salaam, Tanzania

SJOQVIST, F. Clinical Pharmacology Laboratory, Huddinge Hospital, Huddinge, Sweden

SLAMET, L.S. Sub-Directorate of Drug Registration, Directorate General of Drug and Food Control, Ministry of Health, Jakarta, Indonesia

SORDI SABATINI, A. Ministry of Health, Rome, Italy

SOUCHEIRON, C. Laboratorios Dr. Esteve S.A., Barcelona, Spain

SOUSLOVA, O. Russian Centre for Drug Expertise, Moscow, Russia

SRIPAIROJ, A. National Adverse Drug Reaction Monitoring Thailand, Technical Division, Food and Drug Administration, Ministry of Public Health, Bangkok, Thailand

STARESINIC-SERNHORST, D. Drugs Department, Ministry of Health, Zagreb, Baruna Trenka, Republic of Croatia

STEPHENSON, W. Worldwide Product Safety & Epidemiology, Merck Research Laboratories, Blue Bell, Pennsylvania, U.S.A.

SUMER-TOLDI, D. Pharmaceutical and Chemical Company, "LEK", Ljubljana, Slovenia

SZCZERBAN, J. Office for Research Promotion and Development, World Health Organization, Geneva, Switzerland

TAYLOR, N. IMS International, London, England

TEELING, M. National Drugs Advisory Board, Dublin, Ireland

TEN HAM, M. Drug Safety, World Health Organization, Geneva, Switzerland

THITISATTHAYAKORN, S. National Adverse Drug Reaction Monitoring Thailand, Technical Division, Food and Drug Administration, Ministry of Public Health, Bangkok, Thailand

THOMAS, M. Pharmacology Department, ADR Monitoring Centre, Christian Medical College, Vellore, S. India

TILSON, H. Information and Surveillance, Burroughs Wellcome, Research Triangle Park, North Carolina, U.S.A.

TSUKADA, T. Division of Hematologic Research, Toranomon Hospital, Tokyo, Japan

TURNBULL, A.J. International Union against Cancer, Geneva, Switzerland

VAISSERE, J. Pharmacovigilance, Proctor & Gamble Pharmaceuticals, Issy-les-Moulineaux, France

VENULET, J. Council for International Organizations of Medical Sciences (CIOMS), Geneva, Switzerland

VILARDELL, F. Council for International Organizations of Medical Sciences (CIOMS), Barcelona, Spain

VLAHOV, V. Union of Scientific Medical Societies in Bulgaria, Sofia, Bulgaria

VRHOVAC, B. ADR National Centre, Zagreb, Croatia

WEIDMANN, E. Drug Surveillance Department, Hoechst, Clinical Research, Frankfurt, Germany
WESTERHOLM, B. Ministry of Health, Stockholm, Sweden
WHITE, N. Wellcome Clinical Research Unit, Hospital for Tropical Diseases, Mahidol University, Bangkok, Thailand
WIHOLM, B.-E. Medical Products Agency, Uppsala, Sweden
WILLE, H. Institute of Clinincal Pharmacology, Bremen, Germany
ZHU, Y. National Centre for ADR Monitoring, National Institute for Drug Control, Beijing, People's Republic of China

CIOMS publications may be obtained directly from CIOMS, c/o World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland. They are also distributed by the World Health Organization Distribu-tion and Sales Unit, Avenue Appia, 1211 Geneva 27, Switzerland and are available from booksellers through the network of WHO sales agents. A list of these agents may by obtained by writing to the above address.

Price: Swfr. 25.–