



**Monitoring and
assessment of
adverse drug effects**

CIOMS Working Group Report



Geneva, 1986

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Definition of the Issues

by

J. F. Dunne and Z. Bankowski

The Council for International Organizations of Medical Sciences (CIOMS) is an independent, international, nongovernmental scientific organization established in 1949 under the auspices of the World Health Organization (WHO) and the United Nations Educational, Scientific and Cultural Organization (Unesco). One of its prime functions is to act as a sounding-board for capturing and disseminating informed opinion on new developments in biology and medicine and exploring their social, ethical, moral, administrative and legal implications. Over the past decade CIOMS jointly with WHO has collaborated in a variety of matters of direct concern to manufacturers and prescribers of drugs. Notably, it has produced a **set** of International Guidelines on Biomedical Research Involving Human Subjects, which relate to ethical aspects of medical research and have subsequently been incorporated in statutory provisions in several countries. Also, it has produced a report on Safety requirements for the first use of new drugs and diagnostic agents in man, and International Guiding Principles for Biomedical Research Involving Animals.

The stimulus for these developments derives from a Round Table Conference convened by CIOMS in 1977 entitled "Trends and Prospects in Drug Research and Development". It was acknowledged at that time that, by offering an independent forum, CIOMS could facilitate discussion of policy matters between the research-based pharmaceutical companies and national regulatory authorities, and, when required, convene groups of experts to make recommendations on specific issues.

The various collaborative projects that were subsequently realized have had direct and immediate relevance to WHO's own commitment to therapeutic innovation. With the creation of its research-based programmes in tropical diseases, diarrhoeal diseases, and human reproduction, the Organization has focused much attention on the need for new approaches to the conquest of the principal

diseases endemic in the developing world. Its responsibilities are particularly onerous, since it both promotes and assesses innovative research. Already, several new synthetic drugs and vaccines are under active investigation in man. Should one or more of these ultimately be accepted into routine use, their subsequent performance will need to be examined and assessed in countries that have no system of spontaneous monitoring and where little or no attention has yet been given to epidemiologically-based approaches to the investigation of drug performance. WHO thus shares with CIOMS a clear interest in developing a project concerned with the best use of currently available techniques and resources for purposes of post-marketing surveillance.

The need for such a project, however, is rooted in two additional considerations, namely, the intensity of current public and media preoccupation in highly developed countries with the issue of drug safety, and the need to review the scope and potential of epidemiologically-based approaches and computerized record linkage systems for contributing to the further evolution of drug surveillance. Having regard to the scale on which drugs are used throughout the affluent world, there is little doubt that, within society as a whole, they are perceived as necessary and beneficial. This confidence is fragile, however, and is at risk of erosion unless the public can be satisfied that available resources for assuring the reasonable safety of drugs are effectively deployed. The major objectives of the project are thus to present, objectively and persuasively, the benefits that society as a whole derives from access to modern drugs and vaccines; and to make the case that, unless society is prepared to accommodate to and endorse a philosophy in which remote risks to the individual are accepted as the corollary of modern medical care and further therapeutic progress, the whole basis of contemporary drug development will ultimately founder.

This argument can be propounded with conviction only if assurance can be provided that a responsible and committed effort is in hand to minimize drug-induced injury, and if the risks of such injury can be shown to compare favourably to those accepted in other aspects of daily life. Moreover, it can be projected with sincerity only by candid discussion of the strengths and weaknesses of preclinical toxicological studies as predictors of adverse effects in man; of the evident shortcomings of pre-marketing clinical studies as a basis of establishing the safety – as opposed to the efficacy – of new drugs; and of the inability of spontaneous monitoring systems

alone to assure the prompt detection of all unanticipated adverse effects of marketed products.

Whereas the deficiencies of the situation are manifest, perceptions of how to proceed have developed slowly. There has been reluctant acceptance on all sides of the reality that some aspects of a drug's performance can be definitively established only from cumulative experience of its use in routine practice. Emphasis has consequently been slow to shift, in drug safety assessment, from a primarily experimental strategy based upon rigorous toxicological screening in laboratory animals to a more balanced combination of toxicological evaluation and post-marketing surveillance. However, in recent years, pharmaceutical manufacturers have come to terms with the prospect that they face open-ended and searching reappraisals of the performance of their products throughout their commercial life-span. The impact of post-marketing surveillance on research-based companies is unquestionably evident from the recent and widely publicized withdrawals of several newly-introduced drugs on the basis of spontaneous reports of unanticipated toxicity. Wider application of epidemiologically-based studies could operate to intensify or even to allay this trend, but it will certainly not be without impact.

Unfortunately, post-marketing surveillance offers no simple solution to the difficulties of assuring drug safety. At least part of the problem seems to rest with doctors themselves since there is widespread acknowledgement – and some evidence – that they fail to report many serious suspected adverse drug effects to regulatory authorities. Epidemiologically-based studies can be prohibitively expensive, and experience has shown them to be vulnerable, even in the best of hands, to random and systematic bias, which can frustrate confident interpretation of the results. Who, then, should pay for such studies? Who should be responsible for their design? How should priorities be set? Is it feasible to create a coordination apparatus to ensure an effective deployment of available resources? Moreover, some epidemiological techniques, notably case-control studies, offer a highly powerful statistical approach to the analysis of rare events and provide a means of exploring absolute risks of 1 : 10,000 or less, which in many other circumstances would be accepted without demur. The challenge in these circumstances is not only to demonstrate the risk but also to evaluate what implications, if any, it should have for the continued availability of the product.

These questions may not lend themselves to resolution by consensus, but it is important that they be addressed in open debate, not least because some countries will very soon be in a position to examine, virtually at will, possible associations between drug exposure and subsequent adverse events, by applying record-linkage techniques to existing data-bases originally constructed for other purposes. What implications does this hold for pharmaceutical companies, or for doctors, patients or society as a whole? What assurance can be provided about the quality of the information held in such data-bases? How can control groups best be constructed for purposes of comparison?

A cascade of similar questions presents itself to everyone responsible for, or involved in, drug safety assessment. For this reason CIOMS is providing a neutral forum for discussion of these issues at international level, in the hope that some of them, at least, can be resolved to the benefit of society and to the satisfaction of regulators and regulated alike. This report presents the outcome of a preliminary discussion between experts of various disciplines and persuasions invited to a meeting in Geneva in September 1985. In convening this meeting CIOMS has also created a mechanism that enables representatives of industry, regulatory authorities, and academic experts to examine, open-endedly, the challenges and responsibilities as they perceive them. Subsequent strategy will be determined by the response of the various interested parties to this document.

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Monitoring and Assessment of Adverse Drug Effects*

Introduction

In September 1985 a working group convened by CIOMS met in Geneva to appraise what had been accomplished in the field of drug monitoring and to consider what new directions or modifications might be needed. The meeting was timely, for the point had been reached where it was fully realized by regulators, manufacturers, scientists, and the public that the proper development and use of drugs require adequate quantification of benefits and adverse reactions. The concept of balancing benefits and risks has long been acknowledged, but all too often too little is known about the amount of risk involved. There is now a better understanding of how the information may be developed, and it is in the long-term interest of all those concerned to do so.

In selecting participants and designing the programme, it was decided that only a small group should be convened and that its members should represent the interests concerned. The report of the workshop is intended to serve as a basis for discussion and not as an authoritative document and it is hoped that the debate it stimulates will be continued.

The working group had the following objectives:

- To consider and criticize what has been accomplished to date in the discovery and quantification of adverse drug effects, with particular emphasis on the methods used to obtain information.
- To provide a basis for discussion as to what might be accomplished in the next phase of drug monitoring.
- To consider the implications of world-wide drug monitoring, with particular reference to the needs of developing countries.

* The report of this CIOMS Working Group was prepared by Professor **S. Shapiro**, Chairman of the Working Group, assisted by Dr. **D. Kaufman**, Rapporteur.

- To consider matters of policy and law relevant to the monitoring of adverse drug reactions.
- To help clarify the roles of the various constituencies involved with drug monitoring.

This report is intended to reflect, in a very brief summary form, the views of the members of the group. It will identify the issues on which consensus was achieved as well as unresolved disagreements.

Early in the proceedings it was agreed that the methods of studying the effectiveness of drugs would not be considered. Generally, this topic falls under the rubric of randomized controlled trials and analogous methods. It has been considered in great detail elsewhere; the problems in determining and quantifying efficacy are well known, and sophisticated techniques are available for coping with them. Here, studies designed primarily to study efficacy are referred to only insofar as they are relevant to adverse reactions.

The benefits of any particular drug are usually quite well known at the time of marketing, with the exception of agents which are administered in the long term to reduce the complications of disease, such as antihypertensives or cholesterol-lowering drugs. Agents of the latter type, of course, must continue to be studied for efficacy after they have been marketed.

In contrast to benefits, adverse effects frequently are not known at the time of registration and must be discovered after the drug is in use. Because of this, the main emphasis in the workshop was on the evaluation of adverse drug effects after marketing.

A drug may carry the risk of more than one adverse reaction, and there was agreement that, to complete the risk side of the risk-benefit equation, the total risk of morbidity due to all adverse reactions needs to be known. Furthermore, it needs to be known with acceptable precision, expressed as excess incidence rates (attributable risk, absolute risk, or excess risk), rather than in relative terms. Put in its simplest form, an adequate measure of benefit, as against risk, implies having information about the incidence of beneficial effects as against the combined incidence of all adverse effects.

It was felt important to emphasize that the balance between risks and benefits is frequently not the same in all populations. Levels of acceptable risk may be different, for example, in different groups of drug users (e.g., old and young), or in developing countries, where

the morbidity from tropical diseases is very high, compared with developed countries. Further, there may be a gap between the public perception of the risk due to a particular drug and the actual level of risk. These points need to be kept in mind in considering the issues discussed here.

In subsequent sections of this report, the sources of information on the adverse effects of drugs, both pre-marketing and, more particularly, post-marketing, are evaluated. Special problems of surveillance of drugs taken by healthy people, problems of drug surveillance in developing countries, and relevant legal issues are then considered. Finally, conclusions regarding the future of drug surveillance are presented.

Information on adverse reactions which is available at the time of registration

In general, a few thousand patients at most have been studied at the time that a drug is registered for use. The information obtained is limited to data from controlled trials and from pharmacokinetic and pharmacodynamic studies. In addition, there are usually extensive data on the effects of the drug in tissue and in animal models. It is generally thought that pre-marketing data are of little help in evaluating the adverse effects of any particular drug, but this is wrong. About nine out of ten drugs that fail to reach the market are disqualified because of an unacceptable incidence of serious adverse effects in pre-marketing studies. Further, pre-marketing studies may be the only means whereby common but minor adverse reactions can be quantified in a rigorous experimental setting in which the rates can be compared with those occurring with a placebo or with an alternative drug. Such information can be of great assistance in making rational therapeutic choices when a drug is on the market. Added confidence in incidence rates of such reactions can be gained since pre-marketing trials sometimes have detailed information on compliance.

Pre-marketing studies can also be useful after meticulous evaluation of toxicological data in animals and in humans, as well as evidence from the pre-marketing clinical trials, and may yield clues as to adverse reactions that may be anticipated after registration. Such clues, in turn, may be helpful in devising methods to monitor a drug after it is released to the market. However, the workshop

participants agreed that the evidence from pre-marketing studies may be difficult to interpret.

Of the well-known limitations of pre-marketing studies the greatest is inability to detect important but relatively uncommon side-effects. Other problems include the following:

- The therapeutic circumstances are atypical, in that the populations selected for pre-marketing studies are often substantially different from those given the drug subsequently. Also, a strict protocol for administration of the drug is followed, which may not be duplicated in normal practice.
- Because of small numbers it is usually impossible to evaluate the possible effects in sub-groups (e.g., elderly patients or pregnant women), although in some countries pre-marketing studies in the elderly or other potentially high-risk groups are now required.
- Adverse effects associated with long-term drug use cannot be identified.
- Adverse effects due to drug combinations can escape detection.

Post-marketing monitoring

Post-marketing monitoring (PMM) is concerned with the collection, analysis, and dissemination of information on the occurrence of adverse reactions, or the relative safety of drugs, at any time after they are marketed. The workshop participants did not reach unanimity about the distinctions between adverse reactions, side-effects, adverse effects, and so on. Instead, it was agreed that monitoring is concerned with drug safety as a whole. Adverse reactions may be directly related to the pharmacology of an agent, as understood, or they may be inexplicable in terms of any known pharmacology. Most participants felt that, when reactions are pharmacologically related, PMM should not be directly concerned with deliberate overdosage, such as attempted suicide. There was some disagreement as to whether a complication due to relative overdosage because of inappropriate use should be considered an adverse effect.

Data for PMM have been derived from such sources as reports on adverse reactions, large-scale controlled trials conducted after

marketing, formal epidemiological studies of the case-control or follow-up type in which exposures and events are directly determined within individual participants, indirect correlational studies in which drug-use patterns are related to the incidence of events, and sometimes the investigation of outbreaks.

In recent years there has been some confusion about the meaning of PMM (or post-marketing surveillance) because such surveillance has been assumed to be concerned with the detection of adverse effects, or their quantification, within a year or two of marketing. The working group agreed that this restriction is not useful, and that PMM should have no time restrictions. Adverse reactions to drugs, even those as old as aspirin, continue to be discovered many years after marketing, and are legitimately within the purview of PMM.

It was also agreed, however, that drug regulation sometimes requires that decisions be made about possible adverse effects of drugs in the years immediately after they are marketed. This is particularly the case when a drug is a new chemical entity, when it is likely to be commonly used (with a substantial population potentially at risk), when there are identifiable safety concerns from pre-marketing studies, or when the benefits of the drug are likely to be of borderline value. Formal epidemiological approaches have often not been capable of providing the requisite information speedily enough; this was considered to have been a limitation to the drug surveillance strategies devised to date. It was also argued that it may be necessary to compromise between scientific rigour and the need to obtain relevant facts as quickly as possible. There was disagreement about this, with some participants taking the view that the governing criterion should be scientific excellence, and that it is preferable to obtain valid information after a delay than wrong information rapidly.

For drug monitoring to be carried out well and effectively the atmosphere in which the research is conducted is important. In the past this atmosphere has often been characterized by antagonism, particularly between consumer groups, manufacturers, and regulators. In many ways the situation has now improved, with all those concerned increasingly taking the position that it is desirable to have the fullest possible information about both the efficacy and the adverse effects associated with their drugs.

In the next four sections, the various sources of data for PMM are considered. It was agreed that the sources are complementary, that

each has advantages and limitations, and that all need to be employed in a comprehensive monitoring scheme.

Spontaneous reporting of adverse reactions

Individual reports of suspected adverse drug reactions, either in the medical literature, or made to national monitoring centres or the industry, have been fundamental to drug surveillance from the beginning. In an informal sense, this method of drug monitoring has been in existence as long as drugs have been in use. Apart from instances in which such factors as short intervals between exposure and onset of the effect, exaggerations of pharmacological actions, or the effects of re-challenge have pointed to adverse reactions, spontaneous reports have usually provided evidence of causality only when a rare and usually striking outcome is associated with an uncommonly used drug (e.g., oxymethalon and hepatic tumours). When the disease is rare and the exposure is common, some suspicions of causality have turned out to be valid (e.g., oral contraceptives and liver tumours), while others have not (e.g., Bendectin/Debendox and birth defects). It is in this latter case that spontaneous reports can provide "signals", but such signals generally require evaluation by means of formal epidemiological studies.

As with all techniques of drug monitoring, the more information that is contained in the case history the more likely it is to prove useful for purposes of drug surveillance. It was recommended that case reports of an alleged adverse reaction without any other details concerning the patient or the drug should not be given serious consideration.

There has been some variation in the ways in which different countries have set up formal spontaneous reporting systems. For example, in France physicians are required by law to report all suspected adverse drug reactions; in Sweden it is only required that serious reactions be reported. In most other countries, reporting schemes have been voluntary. In some countries, such as the United Kingdom and Australia, national centres have received the reports primarily from practising physicians, whereas in others, such as Switzerland and the United States of America, the main source of reports of adverse reactions has been the pharmaceutical industry (although the reports originate with physicians). Indeed, in the United States, manufacturers are required by law to report all

reactions that come to their notice. There has also been variation as to the type of reactions reported to the central agencies. For example, the French have required that all reports be submitted, whereas in the United States there has been a shift to concentrating on serious and unusual events: routine reports tend not to receive much attention and are simply filed for future reference.

Some members of the working group thought that spontaneous reporting systems may be most useful immediately after the drug is introduced to the market, since there have been instances where results generated in this way have resulted in the withdrawal of a drug soon after its release. It was pointed out, however, that it is in these circumstances that spontaneous reporting systems may be most susceptible to selection bias and exaggeration of the perceived danger of the drug.

Spontaneous reporting systems have the following advantages:

- They can often provide the first evidence of possible cause-and-effect relationships (hypothesis generation).
- They can cover the entire population and all drugs on the market.
- They often provide the only evidence of association between an uncommonly used drug and a rare event.
- There is no limit to the time after registration when an adverse effect of a drug may be identified.
- They are inexpensive.
- They do not in any way interfere with the prescribing habits of physicians.
- They permit the detailed exploration of individual cases. Sometimes patients can be further studied by means of pharmacokinetic, immunological or other techniques.
- Some participants felt that adverse-reaction registries properly operated could be used to educate physicians about the risk of adverse reactions and thereby improve both medical practice and reporting.

Among the disadvantages are the following:

- With exceedingly rare exceptions, adverse-reaction reports cannot yield reliable data on incidence.
- Particularly as regards commonly used drugs, even the appearance of several case reports does not rule out bias,

rather than cause-and-effect, as the explanation for an apparent association.

- Selective reporting, once a suspicion has been generated and given enough publicity, can create an exaggerated and false impression of the magnitude of a problem caused by some drugs.

For all of these reasons, it was stressed repeatedly that spontaneous adverse-reaction reporting systems are mainly hypothesis-generating schemes, giving little or no reliable information about incidence.

In Scandinavia attempts have been made to cross-refer between data banks such as disease registries and drug utilization files to obtain estimates of incidence. There was some disagreement about the value of this approach. Some of the participants felt that this is only useful in exceptional circumstances, such as when there are remarkably high risks (e.g., Guillain-Barre syndrome following Zimeldine exposure).

Despite the limitations of spontaneous adverse-reaction reporting schemes in being unable to provide estimates of incidence, there have been circumstances where the evidence from spontaneous reporting alone has been sufficient to take regulatory action (e.g., hepatic tumours due to oxymethalon).

It was suggested that spontaneous reporting could be improved in the following ways:

- Emphasis on the education of clinicians and others involved in medical care, and more active sharing of experience between recipients of reports and practising clinicians, such as newsletters and furnishing the reporting clinician with other relevant data.
- Better explanation to clinicians that rare and unusual reactions in particular are of interest.
- Further follow-up of reported cases with more detailed documentation, and perhaps ancillary studies. For example, in the case of suspected hepatotoxicity, further follow-up may improve assessment of causality. The reservation was expressed that excessive follow-up could burden the reporter and thereby inhibit reporting.
- Means of ensuring that hypotheses, once raised by spontaneous reports, are adequately and expeditiously tested.

- More exchange of information among national centres, manufacturers, and the World Health Organization Drug Monitoring Scheme. In this regard, all participants recognized and stressed that the absence of any kind of standardization among countries with regard to the requirements of spontaneous reporting creates needless duplication. Reporting forms should contain a core of relevant information recorded identically which would be readily transferable from one data base to the next.

Experimental follow-up studies

Experimental follow-up studies or randomized controlled trials, when feasible and applicable, remain the "gold standard" in the evaluation of drugs not only for efficacy but also for adverse reactions. In general, they share the advantages of pre-marketing trials, with the further advantages of usually being larger and having somewhat greater, although still limited, capacity to identify long-term drug effects in the normal therapeutic setting.

Statistical "bad luck" aside, randomization has the uncontested advantage of controlling both known and unknown sources of confounding. The avoidance of information bias by "blinding" is also sometimes an advantage, but it is not an absolute one since this can sometimes be accomplished by non-experimental methods. Randomized controlled trials are not primarily a technique of post-marketing monitoring, but occasionally are used for that purpose if massive collaborative studies are undertaken for other reasons, or if trials that begin during the pre-registration phase are continued after the drug has been registered.

Despite the theoretical advantages, practical experience with experimental follow-up studies as a technique of drug surveillance has, on the whole, been disappointing. Quite often the large multi-centre trials have produced confusing results (e.g., cancer mortality in relation to the use of clofibrate). These trials are also difficult, costly, and limited in scope, requiring large organizations and the committed participation of many physicians and their patients. Even when massive they may lack the power to detect quite common adverse effects, especially if the effects are delayed. They can be so time-consuming that the drugs under study may be supplanted by other drugs by the time the results are available. In most instances

they can be contemplated for purposes of surveillance only when they are conducted for other reasons.

Fortunately, valid information on the appearance of adverse reactions can be obtained without resort to randomized controlled trials if the indication for the use of a drug is not confounded with the adverse reaction at issue, and this is usually the case. For example, it is most unlikely that the use of oral contraceptives by healthy women is in any way confounded with the risk of thrombosis, and the association can therefore be documented by means of non-experimental methods. However, in the case where the indication is confounded with the outcome and where the confounding variable cannot be adequately measured, putative adverse reactions can be studied only by means of randomization. For example, oral anti-diabetic drugs are used both to alleviate symptoms and, presumably, to prevent the long-term complications of diabetes. The severity of the diabetes, which both affects the likelihood of using anti-diabetic drugs and is a risk indicator for coronary heart disease, cannot be satisfactorily measured or controlled. Thus, in the absence of randomization, the question as to whether anti-diabetic drugs increase the risk of cardiovascular mortality cannot be resolved.

Non-experimental follow-up studies

For purposes of surveillance, attempts have been made to devise effective non-experimental follow-up studies. These have usually been conducted in two situations. The first concerns drugs usually taken by healthy people to prevent disease or events (such as vaccines or oral contraceptives). This matter will be considered in a later section. The second has been when there has been a perceived need for a follow-up study at the time of marketing, owing to concerns arising in the pre-marketing phase, either because of the nature of the pharmacological actions of the drug (e.g., the effect of cimetidine on acid secretion) or because of other evidence such as that derived from animal experiments (e.g., the teratogenic effects of accutane).

These studies have had varying success. For example, it has been shown convincingly that more than 20% of babies born to mothers accidentally exposed to accutane during pregnancy have serious malformations. However, the experience with cimetidine serves to

highlight the problems that can arise when the indication is confounded with the outcome, or when there is misclassification. The association of cimetidine with pancreatic cancer, for example, is almost certainly due to diagnostic error (misclassification) at the time when the drug is prescribed.

A review of the experience with assembling and following cohorts of drug users has generally revealed that the difficulties are substantial, and that the process is expensive. Studies done before marketing generally involve up to about 3,000 patients. Adverse events that are at all common are usually detected before drugs come on to the market. To be worthwhile, therefore, post-marketing follow-up studies have to involve some 10,000 or more patients if they are to yield information that is statistically stable and of clinical importance.

Follow-up studies have the important theoretical advantage of being able to discover associations between drug exposure and any of a large number of events. In practice, however, screening the data for previously unsuspected associations has not been productive. Generally the decision as to what information should be recorded in follow-up studies has been based, at least in part, on hypotheses derived from earlier human and animal studies, spontaneous reporting systems, reports from practitioners, and other sources.

There was some lack of agreement within the working group about the need for a comparison group of individuals not exposed to the drug under study. Some felt that ideally a comparison group should always be studied at the same time. In principle, however, if an event (such as acute hepatic failure) is exceedingly rare in the absence of exposure, a comparison group is not strictly necessary, and it may be more economical to concentrate available resources on enlarging the size of the exposed cohort. The argument for doing this is based partly on statistical considerations. Even with a cohort of some 10,000 patients, sensitivity to the detection of events having an incidence much lower than 1 in 500 is very limited. With the exception of such drugs as accutane, which has been associated with a strikingly large increase in the risk of birth defects, it has seldom proven feasible to mount follow-up studies large enough to quantify the relation of drug use to such adverse reactions as blood dyscrasias, hepatotoxicity, gastrointestinal bleeding, neoplasms, birth defects and other outcomes, which have been among the main concerns with regard to drug safety. It has

also proved difficult to maintain high rates of follow-up, particularly when long-term drug users had to be identified and when events of concern occurred only long after exposure. Moreover, even if the latter problem did not exist, follow-up studies would be of limited use in evaluating long-term drug effects, because of the time required to document such effects prospectively.

Despite these limitations, it was generally agreed that follow-up studies are useful for ruling out very high risks. Thus, studies with no evidence of association can be valuable. If it is proposed, for example, that cimetidine may increase the risk of agranulocytosis, but no cases of this blood dyscrasia occur in a large cohort followed for one year, it may be judged that the benefits of the drug probably outweigh the risk. This may be justified even if it is true that the drug increases the risk of agranulocytosis, but at an incidence that is too low to be detected by such a study. Further, it may be possible in the future to plan *ad hoc* follow-up studies of such sub-groups as the elderly, or pregnant women, if it is thought that such defined sub-populations may be peculiarly at risk of some adverse effect.

Because of the problems encountered in conducting *ad hoc* studies, attempts have been made to utilize approaches based upon record linkage. In the United Kingdom, Inman and his colleagues have taken advantage of the structure of the National Health Service to assemble drug-exposed cohorts of adequate size through the Prescription Pricing Authority. At low cost they have followed cohorts and identified events recorded by general practitioners; by inspecting medical records and interviewing the practitioners they have been able to control confounding and reduce bias from other sources. Recently, they have shown that the incidence of severe hepatotoxicity among users of benoxaprofen, in general, was low. It is important to note, however, that they lacked the data to evaluate the risk in an important sub-group thought to be particularly susceptible, namely, elderly patients. A drawback to their approach has been that the drug exposure data were not computerized. With the manual methods that they were obliged to use, no more than four cohorts could be assembled and studied at one time.

In the United States of America, the main initiatives have involved the exploration of data bases in which there are computer banks linking drug prescriptions and events, mainly hospital admissions for various illnesses. Such data bases have been developed for administrative purposes (such as inventory control) rather than for research, but attempts have been made to utilize them for PMM.

Some of the earlier explorations (e.g., Kaiser Permanente) used data bases that were too limited in size and scope to be informative. Those which have been explored more recently, such as the Puget Sound Health Maintenance Organization, have also been of limited size, and except for a handful of commonly used drugs it has not been feasible to assemble sufficiently large cohorts to provide adequate information.

Medicaid files have been explored as an alternative source of data linkage, but, although they are a substantially larger source, there have been serious problems of selection bias owing to rapid turnover of membership and its non-representative nature. In general, utilization of computerized data linkage in the United States has suffered from the following limitations to a greater or less degree:

- Lack of adequate information on drug exposures other than as "yes/no" variables (e.g., dosage, duration, frequency).
- Little or no information on non-prescription drugs.
- Inadequate (and sometimes incorrect) definitions of outcome.
- Inadequate or no information on sources of potential confounding.

If problems of scale and precision of information can be overcome data linkage may become an important resource for post-marketing monitoring, but to be effective it will require the following conditions:

- The data bases will have to be large enough to enable adequate sample sizes to be assembled.
- It will be necessary to gain access to the patients and to their medical records. Without precise diagnostic information, access to the detailed medical history, more detailed information on drug use than is generally available in computer files, and information on such confounding variables as cigarettes, alcohol, etc., data linkage can be, at most, of very limited usefulness.

Case-control studies

The case-control approach has been used to document such adverse drug effects as vaginal cancer due to diethylstilboestrol, gastrointestinal bleeding due to aspirin, cardiovascular effects of

oral contraceptives, and endometrial cancer due to conjugated oestrogens. It has also been effective in demonstrating a reduction in the risk of certain outcomes such as endometrial cancer and ovarian cancer in relation to oral contraceptive use. In addition, because from this approach large numbers can accrue it can not only document adverse reactions but also rule them out (i.e., establish safety in quantitative terms – for example, that the use of oral contraceptives does not appear to increase the risk of breast cancer).

The main advantages of the case-control approach are that it can:

- evaluate uncommon events, as well as events occurring long after exposure or only after long-term drug use (e.g., cancers).
- test hypotheses relatively rapidly, even when they involve long latent intervals.
- examine multiple exposures in relation to one outcome (e.g., relation of different analgesics to the risk of gastrointestinal bleeding).
- evaluate risks within specific sub-groups, such as the elderly.
- evaluate risks within strata of varying underlying risk (e.g., the risk of breast cancer in relation to the use of oral contraceptives, according to age at first birth).
- be more efficient and less expensive than follow-up studies designed to yield the equivalent amount of information.

The main disadvantages are:

- Inability to discover unsuspected effects of any given drug when the adverse reaction it causes is not already being monitored.
- Limited or no utility in studying rare exposures.
- Limited utility in studying newly marketed drugs, unless they rapidly become commonly used.
- The ability to estimate directly from the data at hand only the relative risk, not the excess risk (absolute risk).
- Quite commonly, problems of possible information bias in ascertaining exposure.
- Risk of selection bias if case identification is associated with the exposure (e.g., using the fact of oral contraceptive use as a criterion in making a diagnosis of deep-vein thrombosis).

The case-control method is conventionally regarded as being most useful in the *ad hoc* evaluation of specific hypotheses (e.g., whether post-menopausal use of oestrogen influences the risk of endometrial cancer), while perhaps at the same time obtaining information on other exposures (e.g., oral contraceptives). However, the method is adaptable as a surveillance technique for monitoring several diseases at the same time, using a common data-collection instrument and obtaining information about drug use in general. Data obtained in this way may be used for purposes of discovery as well as hypothesis testing. In addition, when specific issues concerning individual drug effects arise, it is relatively simple to collect additional data, modify the methods rapidly, or increase the enrolment of cases of interest (and controls).

The approach lacks the theoretical advantage of the follow-up study's unlimited capacity for discovery of new outcomes in relation to the use of one drug. However, as already mentioned, a follow-up study seldom has had sufficient statistical power to exploit that advantage. Also, the countervailing advantage of the case-control approach of being able to evaluate the risk of a specific outcome in relation to a wide range of drugs is substantial. For example, it can be used to estimate the risk of such conditions as agranulocytosis and aplastic anaemia in relation to not only one analgesic but all analgesics, and then to compare the relative effects of each drug. In addition, other drugs causing these conditions can be evaluated.

As experience with case-control monitoring has developed, the method has been refined. More emphasis has been placed on focusing on diseases of particular concern. For identifying subjects with uncommon conditions, techniques for identifying cases of interest have been developed, such as the use of registries of cancers or birth defects, simple scrutiny of hospital admission lists in order to enrol common diseases, and special case-finding mechanisms (e.g., telephoning coronary care units at weekly intervals to find cases of myocardial infarction in young women). The most recent development has been to set up the case-control monitoring of specific disorders known to be caused by many drugs. The first of these were agranulocytosis and aplastic anaemia, originally studied mainly to evaluate risk in relation to use of analgesics. These conditions now continue to be monitored to discover and quantify associations between them and drug use in general.

For the future development of this approach, it was agreed that

one major drawback needs to be corrected, namely the lack of information on absolute risk. Usually this information can be obtained only indirectly, and it requires an estimate of the incidence of the disease, which usually must be obtained separately. Thus, it sometimes may be difficult to produce reliable estimates of absolute risk. In most circumstances, however, it should be possible to estimate the incidence of the disease under study in parallel with a case-control study, and then to derive valid estimates of excess risk indirectly. This matter should receive close and detailed attention in future work.

It is also possible to foresee the development of methods whereby one of the main concerns about case-control surveillance, the problem of information bias, can be remedied in the future. Computer data-linkage systems will probably one day be large enough (and, for certain diseases, already are) to identify sufficient numbers of appropriate cases (and controls). Ascertainment of drug exposure, at least as a "yes/no" variable, should be feasible and could be achieved without information bias. As with follow-up studies, it must be possible to identify the potential cases from a computer file; have access to medical records, in order to validate the diagnoses and to obtain additional relevant information; and have access to the patients to obtain information that may not be present in the medical record. In addition, it would be necessary to obtain from the patients much more detailed information on drug exposure with regard to duration, frequency of use, etc. If these problems can be satisfactorily resolved, computer data-linkage schemes will become powerful and economical tools for conducting case-control studies.

The surveillance of prophylactic drugs taken by healthy people

There have been certain well-defined situations where substantial public health problems concerning the use of certain classes of drugs usually taken by healthy people, such as contraceptives and vaccines, have been foreseen. Large-scale studies, mostly of the follow-up type, have been organized and have yielded important information. Examples include large-scale studies of contraceptive users in England and the United States of America, and international studies (e.g., the World Health Organization study of clofibrate).

Usually such studies have been complemented by case-control studies focusing on specific hypotheses. The workshop participants felt that it is always desirable to obtain information on drugs of this type well in advance of any perceived emergency. For example, had the appropriate studies of pertussis vaccine been done it would have been possible to obtain a valid assessment of the benefits conferred by pertussis vaccination, as against the risks.

Generally, studies of such drugs pose no special methodological problems. In many respects, these drugs are very amenable to study: they tend to be commonly used, making assembly of large cohorts relatively easy, and also making case-control studies feasible. Also, because the populations of users are relatively healthy, there are fewer problems of confounding, and analyses are more straightforward. In the future development of drug monitoring it was agreed that drugs used by healthy populations should continue to be monitored extensively and indefinitely by all of the methods available.

Drug surveillance in developing countries

Because of the problems posed by tropical diseases in combination with overcrowding, poverty and malnutrition, the evaluation of the relationship between benefits and risks of drugs in developing countries is particularly difficult, since the balance between risks and benefits may be quite different from that in other countries. Nonetheless, selecting drugs that are safe and effective, and carry the lowest risk of adverse reactions, is clearly as desirable in the management of tropical diseases as in that of other diseases.

Tropical diseases affect millions of people in certain regions of the world, including South-East Asia, the Indian sub-continent, Africa, Central and South America, the South Pacific, parts of China, and other places. The burden of morbidity and mortality is considerable. Malaria accounts for about 1 to 2 million deaths a year and there are about 190 million persons at risk. Schistosomiasis affects about 200 million people, African trypanosomiasis is a threat to 45 million, and Chagas's disease in Brazil affects 20 million, with 65 million more people at risk. China, India, and Indonesia account for two-thirds of all cases of lymphatic filariasis, with 6 million active cases; in India alone there are 20 million chronic cases and 360 million persons at risk. Leprosy affects 10 million people. The prevalence of

helminthic infestation is not known but many years ago it was estimated that about 800 million people were affected, and that number must now be considerably larger. Amoebiasis is also widespread. Onchocerciasis leads to blindness in thousands of people in Africa and some other parts of the world.

This brief sketch is enough to illustrate that the number of people suffering from, or at risk of, tropical diseases, and therefore requiring drugs, is staggering. Besides, reinfection after a cure is extremely common, and therefore repeated treatments are needed.

Since many tropical diseases are caused by parasites, and since many require vectors such as mosquitoes, preventive measures, in theory, offer the prospect of eradication or reduction of the danger. In practice, however, preventive measures are expensive and slow, and they tend to lose ground because of such pressures as a growing population and limited economic resources. Under such circumstances, chemotherapy is one feasible approach used widely in the developing world. Because the benefits of drugs used to treat tropical diseases are so great in developing countries, the risk-benefit ratio is usually strongly favourable, even when there is a relatively high incidence of adverse effects.

In addition to tropical diseases, many of the common diseases of the developed countries are also prevalent in the developing countries. The magnitude of the health problems and the inadequacy of any infrastructure to deal with them are so great that the monitoring of adverse drug reactions must receive a low priority. The problem is aggravated by lack of funds.

As well as low priority and lack of funds, there are numerous technical obstacles to formal drug surveillance in developing countries. They include a relative lack of qualified professionals, in particular epidemiologists and clinical pharmacologists, generally poor medical records, and difficulties in keeping track of individuals who are enrolled in studies. As a result, follow-up studies are exceedingly difficult to conduct, especially if they are large. Case-control studies are more practical (although still difficult), since they are relatively quick and usually only require one contact with each subject. Spontaneous reporting systems are certainly feasible and should be implemented, but do not usually provide quantification of risks.

Given the background problems the workshop participants suggested a number of strategies.

Certain drugs carry an extremely high risk of morbidity, such as

suramin, used in the treatment of onchocerciasis. It results itself in blindness in about 20% of recipients. This must be compared with the risk of blindness induced by the parasite. It was agreed that relatively small follow-up studies should be sufficient in such circumstances to obtain the data needed to establish a sensible assessment of risk. It was also agreed that certain drugs that are likely to be widely used require evaluation in developing countries if they are not used elsewhere. For example depot-medroxyprogesterone acetate is a widely used and popular contraceptive agent in many developing countries. The safety of such an agent can and should be evaluated, mostly by the case-control approach. Despite the difficulties, such studies have been shown to be feasible in developing countries. The World Health Organization has played an important role in such studies and will continue to do so.

It was suggested that, for the surveillance of drugs commonly used in the developed countries, developing countries need not duplicate the work already done in those countries. Rather, it should be possible for members of government regulatory authorities in developing countries to be trained to evaluate evidence generated in developed countries, and then make their own judgements about its applicability in their countries.

It was also suggested that WHO should assist in the training of epidemiologists and other professionals to devise approaches to drug monitoring appropriate to the environments in which they are to be used, on the basis of day-by-day experience in these environments.

Finally, the hope was expressed that the pharmaceutical industry would assist in funding drug surveillance in developing countries.

Legal issues

Legal issues were considered only in so far as they are relevant to the monitoring or assessment of drug effects and to the orderly development and use of drugs. There is extensive diversity, at the national and international level, of existing and anticipated systems for the compensation of subjects of drug-related accidents. This ranges from redress through the courts, as in the United States of America, to government-sponsored systems of total compensation, as in Sweden. It was felt that CIOMS was not a suitable forum for

formulating proposals in this field, which could best be dealt with by governments and other competent agencies.

Nevertheless, all participants expressed concern over recent developments. Very substantial damages have been awarded to plaintiffs, even in the absence of evidence of a causal association between the use of a drug and the event complained of. Even where a drug has been exonerated, as in the case of Bendectin (Debendox), litigation may substantially distort its development or use. While Bendectin has not been judged to be teratogenic, the manufacturer has withdrawn the product from the market because legal expenses exceeded profits.

Rising liability awards, and the consequent difficulty in obtaining risk coverage, tend to hamper drug development and marketing. While members of the working group agreed that individuals should be able to obtain compensation for injury and loss suffered as a result of the unanticipated effects of the administration of drugs, they noted that reasonable legal restraints were needed, particularly in the United States of America.

The future of drug surveillance

The members of the working group were generally unanimous about recommendations for the future. Above all, they stressed that no single strategy can provide all of the answers needed if drugs are to be adequately monitored after marketing. Instead, drug surveillance must be conceived of as an array of complementary strategies.

Spontaneous reporting

Spontaneous reports will continue to play a major role in drug surveillance. Some attention should be given to how "false alarms" can more effectively be avoided. It was suggested that spontaneous reports could be made more productive by confining them to serious rather than trivial events. There was some disagreement on this point, with some participants taking the view that all adverse reactions should be reported, along with an indication of their "seriousness".

It was also felt that the motivation of reporters could be improved by means of newsletters and appropriate responses to them when

they submit reports. Since the most valid and acceptable spontaneous reports are those which are documented with the greatest rigour and detail, reports consisting of nothing more than allegations without details (timing, use of other drugs, etc.) should be given less serious consideration.

It was recommended that representatives of industry and governments should convene in a separate workshop, to consider ways of standardizing government reporting requirements in order to define the type of information sought and reduce paper work.

Finally, it was suggested that a more free exchange of information among all involved parties, manufacturers, regulators and others, would increase the value of spontaneous reporting.

Experimental follow-up studies

Randomized controlled trials will continue to be useful, particularly for quantifying common adverse effects, and for valid documentation of outcomes confounded with the indication for drug use. It is difficult, however, to foresee any material reduction in the costs of such studies, particularly if they are large-scale. For purposes of drug monitoring it will be desirable to utilize trials of adequate size mounted for other purposes.

Non-experimental follow-up studies

Without question, drugs commonly used by relatively healthy segments of the population must continue to be monitored by the follow-up approach. This applies particularly to such drugs as contraceptives and vaccines. Existing studies of contraceptive use, for example, should be continued indefinitely.

Follow-up studies conducted through data linkage could become one of the major resources of drug surveillance if some of their disadvantages can be overcome. It is reasonable to project that computer files of drug and diagnostic information will become increasingly prevalent, so that massive data banks will be available. Epidemiologists can play a useful role if they participate in the design of such data banks, so that they can more readily be used for purposes of surveillance. When it comes to the efficient assembly of cohorts exposed to specific drugs, this resource may prove indispensable. To be useful, however, automated systems will

sometimes need to encompass millions of individuals, and for reasons given earlier in this report it will be essential to have access to both the patients and their records. In addition, access to computer data-bases must be at a reasonable cost.

Apart from data linkage, there is an urgent need to explore other economical ways of conducting follow-up studies. It should be noted that the two functions, assembly and follow-up, can be separated. Cohorts may be assembled, for example, by recruitment in doctors' offices, in pharmacies, antenatal clinics, etc., depending on what is most practicable. Similarly, independently of how they are assembled, they may be followed up by telephone, mail, clinic visits, and other means.

Case-control studies

Case-control surveillance as at present organized should continue to monitor such outcomes as serious illnesses and birth defects. In addition, since drug usage patterns vary internationally, consideration should be given to the feasibility of international collaboration.

Further refinement of case-control surveillance should be in the direction of the monitoring of illnesses known to be caused by many drugs, beginning with the more common. For example, gastrointestinal bleeding is quite common, and several analgesics, as well as other drugs, are known to increase the risk. Surveillance should be designed to monitor this illness in order to determine which drugs increase the risk, and to compare their respective effects. Other illnesses that should be monitored include peptic ulcer, blood dyscrasias, hepatic disorders, renal failure, and severe dermatological conditions such as the Stevens-Johnson syndrome.

Other illnesses will need to be selected for *ad hoc* study from time to time when suspicions arise. This will apply particularly when it is impossible to distinguish between coincidence and cause-and-effect (e.g., Reye's syndrome in relation to aspirin use).

Apart from the surveillance of relatively rare conditions known to be caused by drugs, the monitoring of common illnesses of major public health importance, such as breast cancer, should continue.

Whenever possible the emphasis in case-control monitoring should be shifted from relative to absolute risk. This should be feasible if the incidence of the disease under study is estimated at the same time.

Finally, it is possible to foresee case-control surveillance functioning in tandem with data linkage, thereby overcoming some weaknesses of both – increasing efficiency, reducing costs, and, in particular, obtaining unbiased information concerning drug exposure. However, it should be stressed that data files may have to be extraordinarily large to be useful.

General recommendations and conclusions

Other recommendations of a more general nature were made. Among them were the following:

- There is a need for a more epidemiological orientation among all concerned – regulators, manufacturers, physicians and consumers.
- Unique problems arise when drugs are first introduced to the market, when concerns about safety need to be addressed quickly. Thus, there is a need to consider how valid epidemiological studies, perhaps of low intensity, can be completed rapidly in order to generate data soon after a drug is introduced to the market. However, to the degree that rapid studies are not feasible, it must be recognized that the acquisition and analysis of valid scientific data often take time and that regulators must resist unreasonable public pressure.
- Monitoring systems should emphasize and quantify the relative safety of particular drugs as well as their adverse effects.
- Drug monitoring cannot be better than the professional standards of those engaged in the work. There is an urgent need to train more drug epidemiologists. Similarly, there is a need for international collaboration, not only in sharing data but also in exchanging ideas about methods of drug surveillance.

Throughout the group's discussions, references were made to the cost of drug surveillance. It was the general view that, although a certain amount of financial support could be expected from government sources, it would be limited, and that much of the support must come from manufacturers. In the long term it is in the interests of industry as well as other constituencies, including society as a whole, to have valid information on adverse effects.

Finally, it should be accepted that no drug monitoring system can ever be perfect. New harmful effects of such a drug as, for example, aspirin continue to be discovered many years after their introduction. Adverse effects are likely to continue to occur and some of them will elude detection even with the most efficient drug monitoring systems. This recognition, in turn, implies that the methods of drug surveillance must continually be reviewed and, as far as possible, improved.

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