Harmonisation in Pharmacovigilance

I. Ralph Edwards and Cecilia Biriell

World Health Organization Collaborating Centre for International Drug Monitoring, Uppsala, Sweden

Throughout the world there is considerable activity in the area of drug safety, pharmacovigilance and pharmacoepidemiology. Considering this first sentence alone raises relevant issues: is drug safety synonymous with pharmacovigilance?; is pharmacovigilance part of pharmacoepidemiology or vice versa? Whilst appearing trivial in one sense, such issues have led to heated debate and to the initiation of duplicative societies and even journals which do not seem quite clear of their subject area.

Considerable confusion has arisen out of the use of various terms in day-to-day work. The most obvious example is the use of ‘adverse reaction’ and ‘adverse event’. The use of the first in relation to a drug has clear implications of causality (or imputability), whilst the second was introduced to allow all clinical changes to be recorded whilst a patient is taking a drug without any implication of causality by the drug. This logical difference is particularly important in collecting information on new drugs where the need to pick up unexpected signals (or alerts) is paramount.

Unfortunately, the above two terms have been seen by too many as being synonymous, with the result that ‘adverse experience’ has been proposed as a substitute for ‘adverse event’ in an attempt to avoid confusion. However, apart from introducing a new complexity, there are now many who use the expression ‘adverse drug experience’. The added word seems to imply causality and will therefore ruin this new term for the purpose for which it was intended.

This introduction should convince the reader of the need to use terms precisely and in a consistent way.

This paper will initially address the use of general terms in pharmacovigilance and also adverse reaction terminology. In both areas it seems better to state our preferences, as far as possible based on widespread agreements, rather than to cover all expressions that are used in the area. We will, however, try to indicate areas of debate and how such debate may be resolved.

In the area of methodology for adverse drug reaction monitoring, there is in our view no need for harmonisation in data collection in spontaneous reporting because there is no current ‘gold standard’. On the other hand, there is a need for harmonisation of data fields which can be easily transmitted between national centres and the industry, so that information on adverse drug reaction (ADR) signals can be analysed expeditiously. Also, pharmacoepidemiological effort needs to be more concerted in order to avoid expensive duplication in signal follow-up. These issues and current endeavours for their management will also be reviewed.

I. General Terms in Adverse Drug Reaction Monitoring

As mentioned, there is considerable doubt about what is meant by such terms as ‘signal’, and causality terms such as ‘probable’. Some authors define the terms in their own publications but in
others it remains unclear exactly what the author means.

Early in the development of the WHO Programme on International Drug Monitoring the term 'adverse reaction' was defined as 'A response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function' (World Health Organization 1972).

Since then there has been pressure to change this definition, for instance to include overdose. The reasonable rationale that a normal dose in one person may be an overdose in another argues for this. This may have the consequence that all those involved in ADR monitoring would also have the responsibility to record the clinical data from suicide attempts and other cases of drug abuse, since clinicians would have some difficulty in deciding what cases were reportable. Perhaps it would be possible to deliberately exclude such drug misuse from ADR data files, but then what about accidental overdosage by patient or prescriber error?

The purpose of mentioning these consequences is to draw attention again to the importance of definitions. The argument that the definition should be changed would probably improve drug safety monitoring as a whole because more information on unwanted drug effects could be collected and collated, but at what cost? An addition to the definition which includes overdosing during clinical trials has been made by the European Commission (1988). Most of the other published definitions are at least in keeping with the original WHO definition in intent. However, the US Food and Drug Administration (FDA) definition of reportable adverse reaction as 'Any experience associated with the use of a drug whether or not considered drug-related and includes any side-effect, injury, toxicity or sensitivity reaction or significant failure of expected pharmacological action' (US Food and Drug Administration 1985) causes confusion with 'adverse event' by explicitly excluding a causal relationship as being essential. The FDA definition also adds another controversial parameter, namely lack of expected effect.

2. Definitions

In an attempt to agree on a truly international definition of regularly used terms in the pharmacovigilance area, the WHO Programme canvassed its members for lists of the terms they used regularly and their own definitions. After several attempts, the following harmonised versions were agreed upon and circulated within the membership (Delamothe 1992). Since these definitions have never been widely published in their entirety they are reproduced in full below. They are as adopted by National Centres participating in the WHO International Drug Monitoring Programme, September 1991.

*Side effect:* any unintended effect of a pharmaceutical product occurring at doses normally used in man, which is related to the pharmacological properties of the drug.

*Adverse event/Adverse experience:* any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

*Signal:* reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information.

*Adverse reaction:* a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.

*Unexpected adverse reaction:* an adverse reaction, the nature or severity of which is not consistent with domestic labelling or market authorisation, or expected from characteristics of the drug.

Other WHO definitions relate to causality assessment of suspected adverse reactions.
Certain: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmaco logically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

Probable/Likely: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

Possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

Conditional/Unclassified: a clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data are essential for a proper assessment or the additional data are under examination.

Unassessable/Unclassifiable: a report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Since then there has been further consideration of some terms by other international groups, notably the Council for International Organizations of Medical Sciences (CIOMS), which has both national centre and pharmaceutical industry representatives, the International Committee on Harmonisation (ICH), which also has both industry and governmental administrative representatives from the USA, Japan and the European Community. As examples of these activities a CIOMS working group is considering, amongst other issues, terms which relate to the frequency of ADRs, e.g. what is ‘frequent’? Is it 1 in 100 or 1 in 1000, and does ‘common’ mean the same as ‘frequent’?

The ICH has produced a definition of ‘serious’ that distinguishes it from ‘severe’. The former is held to relate to the outcome of an ADR whereas the latter is a grading of the degree of any ADR; thus a severe pruritus is not a serious adverse reaction.

On the whole, the variations on previously well-known definitions which have been suggested by these international groups have been minor. For instance, consider the Committee for Proprietary Medicinal Products (CPMP) of the European Union ‘Notes for Guidance’ 111/3978/88-EN for ‘adverse event’: ‘Any undesirable experience occurring to a subject during a clinical trial, whether or not considered related to the investigational product(s)’ (European Commission 1988). Also, the proposed ICH definition (International Committee on Harmonization 1994): ‘Any untoward medical occurrence in a patient treated with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment’ is very similar.

The most different is that of the International Federation of Pharmaceutical Manufacturers Associations ‘Adverse event: a noxious and unintended clinical occurrence or laboratory test result, observed in a patient receiving a drug, which is related in time but is not necessarily caused by the administration of the drug’ (Stephens 1992), but it will be seen that it is the detail rather than the general thrust of the definition which is different.

As might be expected, where there have been differences and debate over definitions historically, these are reflected in marked variations in the latest proposals by international groups of experts. The different professional composition of the dif-
different groups has lead to some important discrepancies in important definitions. Consider the WHO causality terms, which were heavily based on those proposed by Karch and Lasagna (1975), and compare them with the European Commission Pharmacovigilance Working Party's terms (European Commission 1993).

A – Probable: reports containing good reasons and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely, but not necessarily highly probable.

B – Possible: reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible and not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence.

O – Unclassified: reports where causality is, for one reason or another, not assessable, e.g. because of insufficient evidence, conflicting data or poor documentation.

It is clear that the WHO definitions strongly imply that a clinical judgement has to be made and that those cases where there is too little information should be regarded as 'unclassified' or 'unclassifiable'. The EC definitions of 'probable' and 'possible' are mainly concerned with the amount of evidence available for a clinical judgement to be made and give no detailed guidance on how each classification should be fulfilled. It is very likely that the use of these two systems would result in very different attribution.

Apart from the differences in some existing definitions giving rise to concern, there are new terms or uses of terms which need to be considered. To give a single example, the term 'withdrawal syndrome' has been considered by many to refer to a psychological and physiological state resulting from the discontinuation of drugs of dependence, but there is increasing use of the term to describe rebound following the use of drugs that act on receptors anywhere in the body.

WHO has a large part to play in accomplishing this task with the best compromises that are possible. It is in the interest of all that drug safety is not bedeviled by the enshrinement of definitions into legislation or strong guidelines which are confusing or different in a significant way between countries.

A very good and recent review of definitions used in pharmacovigilance is given by Stephens (1992).

3. Methodology in Drug Safety Monitoring

3.1: Spontaneous Reporting

It has frequently been stated that monitoring spontaneous reports of ADRs is the most cost-effective and indeed the only practical way for general drug safety evaluation postmarketing. Different ways of encouraging professionals to report their ADR experiences have been tried, but underreporting remains a major criticism, together with lack of controls, difficult or impossible quantification, and the openness to many forms of bias. With these latter criticisms one may wonder how useful the data are, and whether any of the problems can be adequately addressed. The answer to both these questions depends upon what one wishes to achieve with a drug safety monitoring programme.

The information available on registered drugs has a wealth of detail on pharmacological action, toxicology and clinical experience for the primary clinical indication, to give a reasonable idea of how a patient's health may be improved. Similarly, the chance of harm up to a frequency of about 1 in 1000 patients exposed to the drug is possibly available from premarketing drug evaluations with good controls, although about 3000 patients are needed to be fairly sure of finding one adverse reaction with a random risk of 1 in 1000, if the background risk is zero.

The information missing from premarketing studies is firstly that which might identify people particularly at risk; that is, clinical trials in special disease subgroups more likely to be using the drug or at risk from adverse effects. This situation is
changing. Recently, for example, we have seen more clinical studies in the elderly and certain disease states such as liver and renal disease, where these seem clinically relevant. However, there are almost no studies in children or in women in premarketing evaluations. This is sometimes said to be for ethical reasons, but what is worse than having to use a drug without scientific evaluation? At least we could ask for special postmarketing monitoring of and reporting for drugs when used in children, even if we do not want children included in clinical trials.

The second major area of missing information after premarketing studies is the full nature and extent (i.e. expression) of the known harmful aspects of a drug. When a drug is marketed, experience with adverse effects occurring in less than 1 in 100 patients is too small to be sure of the full expression of an adverse reaction. Even attribution of causality might be debatable for some events which have a high background incidence in the population. If events have an incidence of less than 1 in 1000 they may not even be seen in premarketing studies. Most agree that more extensive premarketing trials, before the drug is tried in normal clinical practice, will provide little or no greater security and at an unacceptable cost both financially and perhaps in terms of delaying a useful treatment option becoming available. Whether greater safety information should be required on new drugs where there are already enough alternatives for the same clinical indication and whose only advantage is a claimed better safety profile has to be debated.

Postmarketing monitoring systems, gathering spontaneous reports of adverse drug reactions, were evolved to improve this situation, with the philosophy of pooling individual ADR experience on a national and international basis so that emerging safety issues could be dealt with expeditiously. In other words, the databases were evolved to collect suspicions (or signals) of problems during routine clinical use. That there is no real quantification of rates of suspected reactions possible, and that remote, objective causality ascertainment may be difficult or impossible is of less importance in the context of raising an early suspicion. Heterogeneity of drug use and also of the reporters' professional backgrounds is a positive advantage, since the drug is being observed and tested under a whole range of clinical conditions.

Indeed, the only factor that really counts in this system is that suspicions of new problems with drugs should be well reported, collated, and then evaluated by experts against what is known from previous experience with the drug.

Much discussion has taken place over various algorithms to aid causality assessment (Stephens 1992). It is fair to say that there is no consensus on their use, but they are more time consuming than clinical expert diagnosis. One major value that they have is to encourage the collection of relevant information in making an assessment. They are thus useful in harmonising assessments, say, between regional centres.

Given the above comments, harmonisation in spontaneous reporting should concentrate on methods that will enhance reporting rates, the amount of useful case information collected and thoughtful differential diagnosis in individual cases.

Many ways to improve reporting have been suggested and some are given in table I. Generally speaking, good communication by a centre with medical professionals is the way to achieve this. It is agreed by most of the professionals working in national ADR reporting centres that feedback on

<table>
<thead>
<tr>
<th>Table I. Ways of improving reporting of adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Easy access to reporting forms</td>
</tr>
<tr>
<td>Facilitate reporting (e.g. by computer links)</td>
</tr>
<tr>
<td>Acknowledge receipt of reports</td>
</tr>
<tr>
<td>Feedback to reporters</td>
</tr>
<tr>
<td>Publish articles in medical journals</td>
</tr>
<tr>
<td>Participate in scientific conferences</td>
</tr>
<tr>
<td>Encourage reporting by clinical pharmacists</td>
</tr>
<tr>
<td>Include adverse drug reaction monitoring in student education</td>
</tr>
<tr>
<td>Form regional centres</td>
</tr>
<tr>
<td>Get in touch with professional organisations</td>
</tr>
<tr>
<td>Create institutes of clinical pharmacology</td>
</tr>
</tbody>
</table>
individual reports and useful clinical publications from the centre enhance all aspects of reporting. Regionalisation, where the national population serviced is large (perhaps over 3 million), may be a way of maintaining good communications. There is evidence that compulsory reporting probably does not enhance reporting long term. Encouraging concentration on key drugs is practised in some countries, but the value of this is not established.

In contrast to leaving a good deal of flexibility for primary reporters to submit what cases they think may be important, it seems very rational to harmonise the data fields that are extracted from reports of suspected ADRs and then used to exchange information between ADR reporting centres. There is a WHO standard reporting form, which is also supported by clear instructions about how the different fields are to be completed. This is currently used by 38 member countries of the WHO Programme for International Drug Monitoring to present their data for storage in the international database.

It is clear, however, that many other groups interested in collecting ADR data have their own forms and data fields, which are completed in a variety of ways. If data held by the different groups need to be pooled or compared there may be delays and confusion caused by such issues as checking for duplication, and any kind of computer aided analysis of data is much easier with harmonised data fields. A working group of drug regulators and industry, under the umbrella of CIOMS, is currently investigating the possibility of harmonisation of data fields.

In order to overcome some of the drawbacks of spontaneous reporting, prescription event monitoring (PEM) and postmarketing surveillance (PMS) have been introduced, both with the general philosophy of following up all patients, or a large representative unselected cohort of patients, exposed to a new drug after launch onto the market. The use of patient cohorts derived from prescription monitoring as used in New Zealand (Intensive Medicines Monitoring Programme, IMMMP) and Britain have proved effective in compiling safety profiles for new drugs, and have the advantage of being able to assess benefits at the same time as risks, as well as determining secular trends for both. Prescription monitoring allows the follow-up of all the users of a new drug by questionnaire for any untoward clinical event, thus avoiding the problems of selection of patients, reducing underreporting of events and avoiding premature attribution of causality in single patients. Large cohorts of patients of, say, 10 000 can be assembled, but in general no properly comparative control group is used: monitored patients with the same disease but on other drugs are sometimes used as controls.

PMS has the advantage of being able to recruit a control group since the patients are recruited through a large panel of prescribers, but there are potential problems of selection bias in recruitment, and of getting large enough study numbers to reach conclusions on safety (Waller et al. 1992). Good study design and planning can avoid most problems.

If more than one such study is running at the same time, for the same drug or even indication, there is a clear possibility for competition in the enrolment of both prescribers and patients. Since the aim of both PEM and PMS is to recruit as many patients as possible after the launch of the new drug, cooperation to avoid this seems desirable.

3.2 Follow-Up of Signals

Contrary to the proposal that harmonisation in spontaneous reporting should be limited so as to preserve the freedom of hypothesis generation, there should be much more standardisation in the methodology of signal follow-up.

More recently, pharmacoepidemiology has come to the fore in drug safety because cohort and case control studies, both prospective and retrospective, allow for quantitative risk estimation from controlled comparisons. The case control methodology has been seen as particularly attractive because data from existing disease databases, either multipurpose or specialised, can be used to obtain relatively quick and inexpensive results. Prospective cohort studies are on the whole more
expensive and take longer to produce information. It is clear, however, that there are many instances where the latter are more appropriate, such as when the background rate of the event is high, exposure to the drug in question is limited, and where information on potential confounders may not have been routinely collected.

Given that pharmacoepidemiology has an important place in drug safety, a pivotal question is how quickly can one investigate an early signal of a problem with a drug using appropriate techniques. The more practical approach is to use data which are continuously and reliably collected which will identify all relevant patient information, including all drug use and disease information. Hospital discharge registers, such as those first developed in the Nordic countries, have proved valuable for studies in pharmacovigilance. The multipurpose disease-based registers currently used increasingly for these sorts of studies in a more general patient population, are mainly available in North America, but are being developed in Europe.

One area for some uniformity in pharmacovigilance is therefore to try to work towards international cooperation for signal analysis using the above pharmacoepidemiological tools. A corollary to this is that countries should work towards improved disease databases and the training of pharmacoepidemiological experts. The WHO Programme data show differences in the ADR profiles for the same drugs in different countries, and there is a need to investigate whether these are due to spontaneous reporting artifacts or are due to real differences in drug use or population sensitivity.

It is clear that it is not reasonable to investigate all new drug-adverse reaction relationships, and some measure of agreement over how to utilise pharmacoepidemiological resources seems advisable. Suspected ADRs, particularly of a serious or potentially serious nature, which have not been seen in premarketing studies should be assessed for incidence, by some rough approximation using drug utilisation data. Those with incidences apparently less than 1 in 10,000 patients require evaluation for risk factors and expression of the ADR.

This situation is usually not urgent, and a request for special reporting by practitioners is probably the best tool for this, though careful case control studies may be required if the reaction is potentially serious and if causality is in doubt, for instance, where there is a substantial prevalence of the clinical event due to other causes. Cohort studies are not cost effective because of the time it would take to recruit a large enough cohort to study such rare events. PEM would be a possible alternative, with adequate controls, if an adequate number of users is already registered.

With incidence of occurrence apparently lying in the range 1 in 1000 to 1 in 10,000, an accurate overall idea of incidence and attributable risk is desirable in addition to qualitatively defining risk factors. It is not easy to generalise about the type of study which would be most informative, but the use of computerised databases with a case control method has the advantage of speed and relative economy. These should only be considered for questions where the database information is likely to be reliable and complete; the multipurpose databases are an attractive option. Cohort studies are worth considering when the event suspected of being a reaction has a high stable background incidence. Serious reactions with an incidence between 1 in 1000 and 1 in 10,000 require a rapid multidisciplinary review and analysis because of the clear impact on public health.

It is helpful to consider the temporary suspension of drugs from the market during such investigations, and it is a shame that this often cannot be done without jeopardising a drug’s future, should the investigation prove negative.

The comments on reactions with an apparent incidence between 1 in 1000 and 1 in 10,000 apply even more to new reactions found postmarketing with an incidence greater than 1 in 1000. Rigorous, rapid investigation is essential and, if the reaction is serious, permanent suspension of the drug seems reasonable, even based on spontaneous reports with a rough incidence assessment, to avoid any
further patient exposure. Suspension should not be inevitable, however, since there is the benefit aspect of the drug to be considered as well. Going back to preclinical and premarketing data will provide useful insights, perhaps more importantly in this incidence category.

The continuous monitoring of disease commonly attributed to drugs such as agranulocytosis, seems a reasonable addition to safety monitoring. Such diseases are not so common but form frequent causes for regulatory drug actions. The availability of disease databases would allow for rapid risk assessment, though the cost-benefit of maintaining such databases, with adequate controls, needs examination.

Bearing in mind the need to determine the range of expression of an ADR, whenever any of the above methods are used, a very important consideration is case detail. Clear measures of severity of expression of the ADR must be recorded to give a complete clinical picture as well as the patient's characteristics to determine risk factors as well as complete drug use information. Agreement over the essential report details transferred between national centres was achieved many years ago (World Health Organization 1972), and between the pharmaceutical industry and national centres more recently (Council for International Organizations of Medical Sciences 1990).

Since the advent of electronic information transfer, it has become necessary to review data fields which should be transferred and their format. CIOMS is currently performing such a review with the aim of international harmonisation of report data fields globally.

Signal follow-up should not be confined to epidemiological studies alone. Much could be learned by thorough checking of existing background pharmacological and toxicological information e.g. from animal experiments, which should be reviewed to see if further laboratory or clinical investigation may help in elucidation of risk or mechanism of the putative reaction. Combined pharmacogenetic and epidemiological studies are a good example of interdisciplinary investigation.

4. Consistency in the Use of Pharmacovigilance Data

It does not seem appropriate to stop the availability of all drugs with rare but serious problems, so long as they are effective, unless there are a number of safer alternatives, so that the range of individual idiosyncrasy can be catered for. After all, some drugs with well known and serious risks are available on the open market, such as aspirin. There are, however, important issues over how safety information should be provided both to health professionals and the public.

Putting aside cost considerations, ideally one would use the safest drug; given similar efficacy. Prescribers and patients should therefore want to know something about the relative risk between two products for the same indication. However, even if drugs have a qualitatively similar therapeutic effect, it is difficult to demonstrate quantitative efficacy within a 20% error by the relatively small clinical trials performed before marketing. Since thousands of patients need to be monitored to obtain good risk profiles, it is almost impossible to make accurate enough qualitative and quantitative comparisons of risk-benefit profiles by available methodologies. Moreover, there are many non-drug factors that influence the safe use of different drugs in clinical practice, such as prescriber and patient familiarity with a particular product.

Even though only crude comparisons between the risk-benefit profiles of drugs are possible, comparing risks for adverse effects out of context to the whole profile of the drugs in question is a worse error, particularly relative risks for rare events out of context may give totally misleading impressions of a drug's safety.

There are several common problems in the presentation of ADR information, but two will illustrate the need for agreement in this area. ADR information is usually qualified only by likelihood of causality and incidence. However, expression of incidence should be broken down into time intervals of treatment duration, otherwise there is no idea of risk related to duration of treatment, which may vary greatly between drugs and with some
Harmonisation in Pharmacovigilance

101

ADRs. For example, the risk of anaphylaxis is strongly related to the first dose of a course of treatment, but the incidence of pulmonary fibrosis may grow with duration of treatment to a point where long term therapy is undesirable.

Over-aggregation of data is another problem (Leon 1993). For example, relative risk and attributable risk are increasingly quoted in relationship to ADRs, but both may be misleading. They can be applied to individual ADRs, or to an overall risk. For example, risks from cardiovascular events may be grouped together, hiding important differences in individual events such as arrhythmias and heart failure.

It also is pertinent to point out that expressing results as attributable risk gives the difference in risk compared with a control group, the relative risk being the ratio of two risks. Even a high relative risk due to a drug, for a rare event, may be considered to have little clinical significance; after all, a relative risk of 15 for a event with a prevalence of less than 1 in 10 000 for two products, even if serious, is of probably less importance in the clinical differentiation between the drugs than a relative risk of 1.5 for severe skin rash with a prevalence of over 1 in 1000.

On the whole, postmarketing comparisons of drugs are unlikely to add anything to the knowledge gained before marketing, apart from adding to the list of drugs so assessed. On the other hand, this experience should not be dismissed too lightly since contemporaneous comparisons of new and old drugs are necessary, even given their limitations, to support therapeutic changes. Care should be taken in making sure that the conditions under which comparisons between new and old drugs are made are similar, for instance, the risks of an old drug are much better defined than for a new one, simply because of long experience in a variety of clinical practice situations.

Balancing good efficacy in minor disease against the occurrence of rare serious adverse reactions is another problem area. It is clear that value judgements must be made, the question is by whom? Surely it should be the patient who decides, having been given the correct information in a useable format, together with additional information which is best given by a health professional at a consultation.

Recently, work with decision analysis has focused attention on the components to be considered in embarking on any therapy. Whilst the key to these is the quantification of all risks and benefits involved in the decision tree, the final trade-off between what risk for what benefit a patient will accept is still very subjective. There are, however, tests which have been developed, such as the ‘lottery method’ which allows the patient to consider different balances of risk and benefit until a level of indecision is reached. This could be useful in improving overall understanding of how patients perceive risks in therapeutics, but much depends upon the way information is presented and the context of the test; that is, how confused or stressed the patient may be at the time. Also it is probably too time consuming for routine use.

5. Conclusion

This article has dealt with several areas of pharmacovigilance in which some harmonisation or standardisation can be considered. The use of common terminologies and definitions will make all communication easier; we may even understand what we are talking about!

It is our view that standardisation of spontaneous reporting requirements may have a deleterious effect by limiting the forwarding of ingenious observations which do not fall into the specified categories for reporting. On the other hand, there must be a harmonised approach to early drug safety studies when there is a need to assemble a large representative cohort of patients for study. Competition for patients is probably counterproductive.

The methodology of signal follow-up could be harmonised more through a consideration of the nature of the particular drug-ADR relationship and its crude frequency, when it is apparent that certain methods for further evaluation are more appropriate than others. The rapid availability of a limited
range of techniques for signal follow-up is essential if public health is to be protected.

Finally, there is a need for consistency in information transfer of drug safety data and in decision making. At the moment, in both these areas, there are considerable differences in the way data are used, and this is confusing, not in the least to patients and their advocates.

References
US Food and Drug Administration. 21 CFR 314.80 Federal Register 50 (30): 7500, 1985

Leon DA. Failed or misleading adjustment for confounding. Lancet 342:479-481, 1993

Correspondence and reprints: Professor I. Ralph Edwards, Medical Director, WHO Collaborating Centre for International Drug Monitoring, Box 26, S-751 03 Uppsala, Sweden.