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A Model for the Future Conduct of Pharmacovigilance

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Introduction

At the turn of the millennium, those involved in pharmacovigilance face major challenges to satisfy increased consumer expectations and realize the benefits of the technological age. The existing approach has developed through evolution and appears to be widely accepted. However, there is evidence that adverse drug reactions (ADRs) remain a major cause of morbidity and mortality, and it has been suggested in a recent paper that they caused more than 100 000 deaths in the USA in 1994 and could be the fourth largest cause of death (Lazarou *et al.*, 1998). In particular, the effectiveness of the implementation tools may be limited and, although conceptually pharmacovigilance is a monitoring process, adequate outcome measures have not been developed. It is reasonable, therefore, to question whether the existing model will meet the needs of 21st century drug development.

In 2001 we were involved in a project set up by the UK Medicines Control Agency (MCA) to rethink the process of pharmacovigilance on a scientific basis without preconceptions. First, we constructed a preliminary working model that described the key elements which would be required to achieve the best possible process. Input was then derived from colleagues around the world in other regulatory authorities, academia and the pharmaceutical industry by inviting them to review the working model. Subsequently, each element of the working model was treated as a separate theme and small groups were formed to brainstorm each theme and formulate the development of each area.

Proposed model

The purposes of pharmacovigilance were defined as 'to promote safe clinical use of medicines and prevent ADRs, thereby protecting public health'. It was agreed that the key values that should underpin this work are excellence (defined as the best possible result), the scientific method and transparency. The proposed model (Figure 16.1) defines five elements that are considered essential for pharmacovigilance to achieve excellence. Three of these are

[Image not available in this electronic edition.]

Figure 16.1 Model for excellence in pharmacovigilance (*Pharmacoepidemiology and Drug Safety* 2003; 12: 17–29). Reproduced by permission of Wiley

process orientated: best evidence, robust scientific decision-making and effective tools to deliver protection of public health. Some of these processes already exist but might need to be improved in order to ensure delivery of the most effective system possible. The two other elements, scientific development and audit, underpin these processes, recognizing that excellence cannot be achieved merely by process. In order to demonstrate excellence objectively and underpin audit of all levels of the process, novel methods (or applications of existing methods) for measuring public health outcomes need to be developed. The model does not take into account everything that may be relevant, and there are other dimensions (e.g. legal frameworks, local or product-specific factors) that may require consideration in order to use it.

Description of model components

Best evidence

This reflects the need for pharmacovigilance to be evidence based and that decisions, outcomes and overall excellence will be influenced by the nature and quality of the evidence base.

Use of evidence

Conceptually, there are two broad and opposing approaches to gathering and using evidence: demonstrating safety and demonstrating harm. The former is intrinsically more difficult, since safety can only be demonstrated to a finite degree. Traditionally, pharmacovigilance has been more focused on the assumption that there may be unrecognized potential for harm that has not yet been demonstrated because of evidential limitations, and on finding evidence of such harm. This is not to say that the need for better demonstration of safety in clinical practice has gone unrecognized. Various monitored release schemes evaluated in the 1970s

(Wilson, 1986), the Committee on Safety of Medicines' Working Parties of the 1980s (Grahame-Smith, 1987) and prescription-event monitoring (Mann, 1998) are all exercises that, at least in part, have been based on this approach. However, these approaches have not fully circumvented the practical difficulties involved in demonstrating a greater level of safety.

In terms of demonstrating safety, a two-dimensional model may be used, and this is illustrated in Figure 16.2. The key variables of interest are frequency and time of onset. The focus of this interest relates to serious ADRs. In order to demonstrate a greater level of safety it is necessary to move away from the top left as far as possible towards the bottom right, i.e. to gather evidence which shows that serious adverse reactions are rare and that this remains true in the long-term.

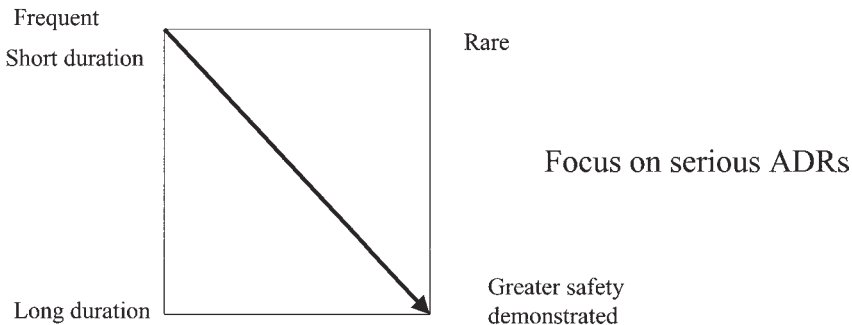


Figure 16.2 Demonstrating a greater degree of safety (*Pharmacoepidemiology and Drug Safety* 2003; 12: 17–29). Reproduced by permission of Wiley

In respect of gathering evidence in pharmacovigilance, it seems that a better balance needs to be struck between the two approaches described above. A mechanism for achieving this would be for a 'pharmacovigilance specification' to be drawn up at the time of marketing authorization. This would explicitly consider the level of safety that had already been demonstrated, possible concerns that needed further investigation and how further evidence was going to be gathered. It would be the responsibility of the applicant to draw up and maintain the specification and it would be analogous to the summary of product characteristics (SPC), in that it would require regulatory approval and become public at the time of authorization.

Evidence hierarchy

A hierarchy of evidence from case reports (the lowest level) through observational studies to clinical trials and meta-analysis is well recognized (Piantadosi, 1995). Higher levels in the hierarchy are associated with a lower degree of uncertainty (in particular regarding causality) and hence there is, in principle, an advantage in moving up the hierarchy as far as possible within practical constraints. Pharmacovigilance tends to rely considerably on evidence from the lower end of the hierarchy (case reports/series and observational studies). Greater use of methods producing evidence at higher levels is a logical aim. The practical

consequences would be more large simple clinical trials and meta-analyses of safety data, both from randomized trials and observational studies.

Spontaneous adverse reaction reporting This is considered to be the cornerstone of pharmacovigilance and the method is undoubtedly of proven value in detecting signals of unrecognized safety issues. Nevertheless, there are several reasons why its future place might legitimately be questioned:

- low level in evidence hierarchy;
- insuperable limitations (e.g. underreporting);
- high resource inputs when considered globally;
- other methods of detecting signals could yet prove superior and/or more efficient.

Our current approach is to develop the method further to maximize its value by targeting areas of weakness, increasing the reporting base and utilizing the data more effectively (Waller, 2000). However, in the longer term, consideration should be given as to whether the method could be completely replaced by other approaches. The critical factor is whether spontaneous reporting adds something unique. If spontaneous reporting does capture something that might otherwise go unrecorded, then it is *suspicious* regarding cause and effect that health professionals considered potentially important. This raises the issue of whether other mechanisms of recording such suspicions in a more systematic way (e.g. prompted by stopping or changing drugs) could be developed that might be more efficient and, therefore, potentially replace spontaneous reporting. In principle, this could be achieved through healthcare databases and the feasibility of the approach should be investigated.

Observational epidemiological research Whilst increased use of large simple trials (see below) would reduce the need for observational studies, these will continue to be required for generating evidence on post-marketing safety. In particular, the inherent time delay can make a prospective trial impractical as a solution to an important safety issue. The goals in this area should be to ensure that high-quality research is conducted promptly and is focused on signals that have potential public health importance. Studies based on the cohort approach have greater potential to extend knowledge of safety than those based on sampling of cases, which tend to focus on the investigation of potential harm.

Standard cohort or case-control studies will continue to be useful, but there are potential modifications to these classic designs that warrant further exploration in this context. These methodologies include case-crossover, case-only and case-cohort designs, and, in some circumstances, counter-matched studies. Each of these can potentially provide gains in efficiency, reduce the time taken to perform a study, increase statistical power or reduce bias. For all of them it is important that high-quality data are available in population-based databases that record, or by record linkage produce, drug exposure and medical events in individuals, together with the possibility of some adjustments for confounding. Data from individuals and not aggregate data must be available for analysis, but the data must be anonymized to ensure confidentiality.

Randomized clinical trials The majority of randomized clinical trials (RCTs) are conducted pre-marketing with a primary objective of demonstrating efficacy. There are three major limitations of the method with regard to safety: obtaining a large enough sample size to study outcomes that may be rare, the generalizability of the findings to ordinary practice, and poor reporting of safety, at least in published trials. Whilst these limitations are important, their recognition has probably led to under-utilization of RCTs for safety purposes. To a considerable degree, both limitations can be overcome by a 'large simple trial' that includes enough subjects to study rare outcome, makes few measurements and imposes no entry restrictions that would not apply in ordinary practice. The logical time to perform such a trial is when the drug is authorized and when uncertainty cannot be resolved through observational studies. The normal unit of randomization is the patient, but cluster randomization (e.g. of general practices) might have practical advantages and is worthy of further exploration, particularly in the context of vaccines.

Meta-analysis Meta-analysis is a well-established technique for bringing together all the valid evidence contributing to a particular question and providing an overall estimate of effect. It has most frequently been used for data from RCTs (particularly in the context of efficacy), but methodologies exist for observational data and are being developed for combining data from RCTs and observational data. Although meta-analysis has critics (particularly when it utilizes only observational data), it is generally accepted that, when based on RCT data, it is at the top of the evidence hierarchy.

The potential of meta-analysis in pharmacovigilance has been underused; for example, no formal meta-analysis of data relating to the differential effects of combined oral contraceptives on venous thromboembolism had been published by the end of 2000, i.e. more than 5 years after the original studies were published. Use of meta-analysis to resolve important safety questions should be a goal that helps to drive the process of investigation. Even when overall estimates could be regarded as misleading (e.g. when there is significant heterogeneity or debate about the validity of some studies), graphical display of all the data on the same scale, with confidence intervals, may be a valuable aid to understanding the overall evidence base, shedding light on reasons for heterogeneity. We envision that meta-analysis of pre-marketing safety data will frequently underpin the pharmacovigilance specification drawn up at the time of authorization.

Basic research and pharmacogenetics

There is potential for preventing adverse reactions, and, therefore, of improving the safety of medicines, through developing a better understanding of the mechanisms of ADRs and the genetic contribution to drug response. Following the success of the human genome project, the identification of genetic predictors of ADRs is now feasible and represents an opportunity that could substantially impact on pharmacovigilance over the next 5–10 years. In particular, it could provide evidence that would allow the prevention of many ADRs, including both those that are dose-related and those that are idiosyncratic. Genetic markers may predict both efficacy and toxicity of many drugs (Ozdemir *et al.*, 2001) with potentially major implications for their practical use and safety. Whilst pharmacogenetics will particularly impact on early stages of drug development, it will also be important to ensure that its methods are applied to drugs that are already authorized.

Data resources

In terms of data resources, the ultimate aim should be the development of a complete population database with well-documented exposures to medicines, outcomes and potential risk factors. In the UK, such a database is unlikely to be achievable for several years, and the needs of pharmacovigilance are unlikely to drive its development. There may also be problems resulting from a drive towards increased confidentiality that may work against the interests of public health in relation to drug safety. As noted above, individual records are vital for analysing the safety of medicines using epidemiological methods. Meanwhile, existing databases should be used to develop and test approaches to maximizing the utility of a total population database. Particular attention should be paid to their predictive value in detection of signals and how to encompass the need for both hypothesis-generation and hypothesis testing in a single database. Since a total population database is likely to be based around primary care, there is a need to ensure that adequate information is available on hospital exposure to medicines and outcomes. The availability of better information on medicines used without a prescription with linkage to medical outcomes also requires consideration (Clark *et al.*, 2001).

Environmental considerations

The most important environmental consideration is the worldwide dimension to evidence that is relevant to pharmacovigilance. There is a major logistic difficulty in bringing all the relevant evidence together in one place. Currently, there are two mechanisms through which this is attempted: the World Health Organization international spontaneous reporting database in Sweden (Olsson, 1998) and periodic safety update reports (PSURs) by pharmaceutical companies – and some relevant standards agreed through the International Conference on Harmonization (D’Arcy and Harron, 1996). In respect of PSURs, they have added a major resource burden, but their impact on the public health objective of pharmacovigilance has yet to be evaluated. Overall, the fulfilment of regulatory requirements (i.e. ADR reporting and PSURs) has become too great a process driver and has diverted attention away from scientific approaches to gaining better evidence. The broad solutions to these issues might be: (a) to centralize further the gathering of evidence and avoid duplication of effort; (b) to refocus industry towards the need to gather better evidence of safety rather than solely meeting process requirements; (c) to ensure that regulatory demands on industry have measurable public health gain.

Interface between evidence and decision making

The conceptual framework of the best evidence model is largely focused on the beginning of the process: the gathering of evidence. In contrast, for robust decision making (see below) the focus has tended to be on the end of the process, i.e. making the final decision on a major issue of risk–benefit. In between there are two other broad areas that could be termed ‘evidence distillation’ and ‘issue management’. Although it would be reasonable to consider the former to be part of best evidence and the latter to be part of decision making, they overlap to a considerable extent and involve an iterative process.

Within this interface there are two potential initial drivers, the detection of a signal (i.e.

the identification of unexpected harm) or the achievement of a milestone (i.e. a specified boundary on the map has been reached).

Handling of signals

When the initial driver is the detection of a signal, there are potentially three further steps, as follows:

- impact analysis
- risk evaluation
- risk–benefit evaluation.

Conceptual frameworks exist for each of these steps and, with regard to the latter, a major international initiative is available (CIOMS IV Working Group, 1998). Since risk evaluation is intrinsically part of the latter process (the only reason for considering it as a separate step is that there may be no need to proceed to full risk–benefit evaluation), our attention has focused on impact analysis. This is a key step which should drive use of resource towards issues that have the greatest potential for public health benefit.

For this purpose the MCA have used the SNIP criteria (Waller and Lee, 1999, see also p. 351), which enable a judgement to be made about the priority that should be given to a signal by considering its strength, whether it is new, the clinical importance and the potential for prevention. This is a pragmatic approach that has some value, but it also has conceptual flaws. In an impact analysis, the output is the potential for prevention (i.e. in this model it is not a factor to be considered separately), which is dependent on four factors:

- causality
- frequency
- health consequences
- risk predictors

The first factor to be considered in the analysis of impact is the overall strength of evidence that the adverse outcome is caused by the drug. This depends on both the nature of the evidence and a global evaluation, it being possible to envisage about five levels to which signals could be readily categorized according to objective criteria, albeit involving scientific judgement. For example, the lowest level would involve a small number of spontaneously reported cases with some plausibility of causality based on the individual cases, but no other evidence and potential alternative explanations for the signal. The highest level would be evidence from a meta-analysis of RCT data. Thus, there should be a clear link with the established evidence hierarchy.

Frequency should be measured both in terms of risk to an individual and the population frequency, for which knowledge of the level and duration of exposure is required. The critical factor should be the absolute frequency expressed in terms of an order of magnitude. A CIOMS Working Group has already proposed such a categorization with five levels from 1 in 10 or more to 1 in 10 000 or less (CIOMS III Working Group, 1995). Such

categorization is broad but this has the advantage that it is usually possible to estimate frequency to an order of magnitude even when only limited evidence is available. However, it does not take into account time and its inherent assumption – that the rate of occurrence of an ADR is constant – is often unjustified. The life-table approach (or Kaplan–Meier plot) is a method that has been little used in this context but should prove valuable in addressing this difficulty.

With regard to clinical consequences (i.e. seriousness), it is also possible to envision categorization on a scale according to the risk of fatality and the long-term impact of the outcome on health and quality of life. This could be driven partly by the specific data available for the drug–reaction association and partly by the known epidemiology of the disease.

With regard to predictors of risk, it is important to consider both who is at risk and when they are at risk, i.e. the temporal relation between start of treatment and onset of the reaction. It is clear that the identification of risk predictors is of great importance in developing strategies to prevent ADRs, but they may be less amenable to simple categorization given the wide range of potential risk predictors and considerations relating to their measurement and modification. Furthermore, data indicating that a particular factor is associated with greater risk may not necessarily imply a causal relationship. Conversely, where it is not possible to identify sub-groups at particular risk, this may simply reflect insufficient statistical power.

Overall, the factors discussed together need to be synthesized into an output that indicates both the public health importance and potential for prevention based on the attributable risk amongst exposed patients. We suggest that an empirical mathematical approach incorporating sensitivity analysis could be developed to support this function.

Milestone achievement

Currently, the pharmacovigilance process is based on temporal milestones (e.g. PSURs are initially required every 6 months regardless of the level of use) with a periodicity that lessens as the product becomes established. The conceptual problem with this approach is that there is no clear link with demonstrating the safety of the product; i.e. knowledge of safety, or indeed harm, may not have been extended at all, but there is a requirement to report to regulatory authorities. In the model we propose, the milestones would be pre-specified levels of exposure that are dependent on the type of drug and the availability of new information which contributes to safety. Arbitrary time periods for safety updates and intensive monitoring of new drugs are replaced by milestones, the achievement of which leads to recognition that a greater level of safety has been demonstrated. Markers analogous to the black triangle in the UK (Committee on Safety of Medicines/Medicines Control Agency, 2000) could be useful (by their presence or absence) in signalling to users that a medicine has a provisional or an established level of safety. The logic of the current link (in the UK) of such markers to ADR reporting requirements can be questioned. In our view, such a link is unnecessary and all ADR reporting could be focused on serious and/or unexpected ADRs.

Robust decision making

The essential steps in going from a body of evidence to a decision are: (1) analysis of evidence; (2) identification of options; (3) decision making. There is greatest scope for

innovation in respect of the latter. Currently, the regulatory model used is for one or more assessors to undertake an analysis and identify options, followed by expert committee review and advice on the decision. Their decision-making process is normally informal (i.e. through discussion and consensus whenever possible). The main aim of this part of the model is to assure the quality of decisions, bearing in mind that, in most cases, a considerable degree of judgement is required taking into account factors such as the strength of the evidence, balance of risks and benefits, and likely effectiveness of potential preventive strategies. Other considerations, such as the precautionary principle, may also be relevant. Pharmacovigilance decisions should take into account all the potential public health consequences of the decision and invariably involve comparison of alternative approaches. The principles involved in risk–benefit analysis have been the subject of in-depth consideration by the CIOMS IV Working Group (1998). In particular, their approach to decision making, which outlines the need for objectivity, equity and accountability, are relevant here and should be incorporated into the model.

In respect of the first two stages of the process, quality is currently assured by two processes: formalized assessment and peer review. Development of check lists based on CIOMS IV might be valuable to underpin the formal assessment process. Regarding decision making, the informal committee model is generally considered to work reasonably well. However, there are two conceptual drawbacks: firstly, decisions are dependent on the particular experts involved; secondly, the assumptions and logic underlying the decision may not be made explicit or adequately tested during the process. For these reasons, as suggested, but not developed, by the CIOMS IV Working Group (1998), we have considered whether a more formal decision-making process involving decision analysis might provide the basis for robust decision making. We have also considered how experts might best be used and the potential roles of other stakeholders in the process.

Formal decision analysis

Decision analysis is a process undertaken prior to making a decision and involves using the available evidence to create a model that defines predicted health outcomes associated with each option under consideration (Lilford *et al.*, 1998). The subsequent decision is informed by, but not necessarily predicted from, the model; i.e. modelling is a way of fully exploring the issues rather than making automated decisions. In order to perform decision analysis it is necessary to define probabilities for each of the outcomes and their value or utilities. In doing so, various assumptions are usually necessary, the effects of which can be tested through sensitivity analysis. Standard methods are available, and these have been used both for clinical and public health policy decisions (Lilford *et al.*, 1998). Their potential for application to pharmaceutical policy decisions has recently been the subject of a published review (Patten and Lee, 2002).

The potential advantages of modelling are as follows:

- increased transparency;
- making reasoning explicit, reflecting complexity;
- clearly identifying limitations of the evidence and uncertainty;
- the impact of all assumptions can be assessed;

- better justified decisions.

The potential disadvantages of modelling are as follows:

- adds time – usually weeks (but limited modelling could be done in hours);
- requires additional resource and specialist expertise;
- the model itself (rather than the evidence) may become the focus of debate/challenge.

We suggest that a first step would be to work retrospectively through complex examples with experts in decision analysis. This will demonstrate whether the method is likely to be of value for pharmacovigilance decisions, following which piloting in practice would need to be undertaken.

Who makes the decisions?

With regard to the role of experts in decision making, we recognize that this is a much wider issue and that pharmacovigilance probably has no special need to be different from other processes that involve going from scientific evidence to a policy decision. Nevertheless, there are grounds to ask whether the current model, where expert committees often play the defining role in such decisions, will survive the intense scrutiny that is becoming the norm for issues involving public safety. Clearly, experts should have a key role in evidence appraisal, and developing and testing assumptions in a formal decision analysis. However, when it comes to making decisions, the role of expert committees could be reconsidered.

A recent trend has been the inclusion of lay members on expert committees, but this does not fully address one limitation of the current model, which is that consultation with stakeholders is very often limited and focused particularly on the pharmaceutical industry. In principle, if decision analysis proves to be a useful tool in this field, then, in theory, decisions could be taken by a group that represents all stakeholders and is supported by experts. Most current models leave the final decision to elected representatives who are accountable to a parliament, thereby introducing a political dimension to individual decisions. In the model proposed (i.e. more transparent decisions involving stakeholder consultation) it could be debated whether such direct accountability would be desirable. Clearly, accountability for the overall process to elected governments would remain essential.

The other major issue we considered was the need for agreement across international boundaries. Whilst it is clear that differing decisions on pharmacovigilance issues around the world are common, the reasons for such differences are not well understood. If greater international consistency is to be achieved then these reasons need to be explored, in the first instance through retrospective study of recent major decisions.

Tools to protect public health

This part of the model involves communicating with, and influencing, users of medicines in order to promote safe use and thereby protect public health. Existing tools for communicating new safety information include product information, drug safety bulletins, urgent letters to health professionals and the Internet. Although the precise effectiveness of these tools is

unknown, there are grounds to believe that they are not highly effective. There is, therefore, considerable scope to develop new approaches to delivery of drug safety information in order to meet the needs of users as fully as possible.

General principles of communication

The Erice report (Uppsala Monitoring Centre, 1998) has laid down basic principles about communication of drug safety information which are widely accepted. In particular, this states that drug safety information ‘must serve the needs of the public’, that it ‘should be balanced with respect to risks and benefits’ and that ‘all the evidence needed to assess and understand risks and benefits must be openly available’. These principles should underpin all provision of information and communication about the safety of marketed medicines. The last is particularly important in ensuring that the whole process is transparent.

Another principle that is widely accepted is that different levels of information are needed to meet the varying needs of recipients. In practice, this has led to a binary division into separate information for health professionals and for patients, which is reflected within the EU regulatory system with respect to product information. However, experience has shown that this approach is too simplistic, since both health professionals and patients have a wide variety of potential needs. Therefore, we suggest that multiple linked levels of information are necessary and that a distinction between information for health professionals or patients is not always necessary. Information provided at lower levels should be presented in non-technical language in order to be understandable to lay recipients. Complex information at higher levels will inevitably need to be presented using technical language. The idea is that users start at the lowest level and progress as far as they wish to according to their information needs (e.g. distinguishing what is needed to be known prior to taking the drug and what is needed to be known while taking the drug) and capability to understand the information.

Although we are proposing to drop the distinction between health professionals and patients in terms of access to information (i.e. the information available to them should be the same), it should be recognized that different approaches to delivery may be necessary in order to influence these groups (see below).

A new approach to product information

When considering these principles further, product information is the logical place to start, since this should underpin all other sources. The current model for product information in the EU is that an SPC in a standard format is attached to the marketing authorization and serves as both a regulatory document and as a primary source of information for health professionals. User leaflets supplied with the medicine are based on the SPC and written in lay language in a standard format. The main disadvantages of the current system relate to the dual purpose of the SPC (it is widely recognized that, although it fulfils well the regulatory purpose, this document is not particularly useful to health professionals) and the considerable constraints on presentation and lack of flexibility resulting from standardized formats for both SPCs and patient information leaflets (PILs). Both these disadvantages tend to result in a lack of impact of key messages, which cannot be presented in an appropriately highlighted way and which are often surrounded by (but not differentiated from) much less important information. A further problem is that basic information is not always easily

accessible to health professionals or to patients before a medicine has been dispensed or purchased.

Therefore, we propose that the SPC (essentially in its current form) should be regarded purely as a regulatory document and that much greater flexibility should be allowed as to how user product information is presented. Potentially, this would lead to greater value to users, and promote safe and effective use of medicines, with a lesser degree of regulation. It should, therefore, be attractive to both industry and consumer groups.

A suitable working model for further discussion might be as follows:

- All product information to be consistent with the SPC (and, therefore, to be amended if the SPC is significantly varied).
- Product information to remain non-promotional.
- Requirements for certain key information (especially regarding safety) to be included and highlighted on all documents.
- Few other constraints on format and presentation.
- Opportunity for regulatory review.
- Underpinning guidance indicating that:
 - product information should be developed by communication specialists, not scientists;
 - multiple linked levels of information should be available, e.g.
 - essential user information with highlighted key messages in lay language (level 1)
 - more detailed information comparable in depth to current SPC (level 2)
 - technical supporting documentation, e.g. assessment reports (level 3) and summaries of data from trials, etc.

In terms of provision of information, the following primary routes are envisioned:

- Level 1 information would be provided with the product.
- Levels 1 and 2 would be provided in compendia of product information (in both paper and electronic forms).
- Levels 1, 2 and 3 would be provided via the internet.

Influencing health professionals

Whilst provision of safety information to health professionals is straightforward, changing behaviour is more difficult. In particular, the necessary information may not be remembered or immediately accessible when it is needed. The most effective way of overcoming this barrier is likely to be through computerized decision support. There is a need to develop intelligent decision-support systems for health professionals to support rational use of medicines, which *inter alia* helps to promote safer use. These will need to factor in individual patient characteristics (e.g. concomitant disease and medication) and provide links to supporting information on the Internet, such as guidelines and expert assessments (e.g. Cochrane reviews).

In addition to effective delivery, there is a need to improve the clarity and impact of the messages by making all information more attractive and accessible (e.g. by including a box with the most important things the prescriber should know about a medicine). It is also important to recognize that the messenger needs a high profile and credibility in order to generate the necessary confidence in the system.

Influencing patients

Users of medicines may require general education on risk–benefit and specific information on the medicine(s) that they use. The information they require may differ before, during and after taking a medicine. PILs provided with the medicine are potentially a valuable tool, but experience to date suggests that they are not seen as user friendly and may cause problems with the doctor–patient relationship. It is difficult to address these problems without fairly fundamental changes, because the format is currently highly constrained by regulatory requirements. In the model proposed above, supply of the lowest level of information with the medicine would replace existing PILs and there would be references to other sources of information, such as relevant Website addresses.

Outcome measures and audit

The functions of this part of the model are: (1) to demonstrate the extent to which the process of pharmacovigilance is effective in the protection of public health; (2) to underpin excellence by enabling improvements to be made which are based on evidence and/or experience (i.e. audit). These goals require substantial innovation, since no well-established outcome measures are in routine use and audit of pharmacovigilance is currently limited and solely process orientated.

Outcome measures

Attempts are often made to judge the effects of interventions using spontaneous ADR reporting data. However, it is doubtful that such data are generally useful for this purpose, because there are several potentially counteracting effects on reporting of sending out a safety message. The sum of these consequences is enormously variable and rarely interpretable with confidence. Complete cessation of reporting of a particular ADR may be taken as an indication of a positive effect, but even this could be subject to bias.

Other previous work in this field has concentrated on the effects of specific recommenda-

tions, often with a particular focus on prescribing. For example, it is relatively easy to measure co-prescribing of interacting medicines for which combined use is contraindicated, before and after warnings are issued. Such analyses, together with spontaneous ADR reports, have then been used to make a judgement as to whether the measures taken were sufficient.

The effects of interventions on usage of medicines is an important surrogate outcome measure that should be much more widely and routinely utilized. The most useful readily available source of data is prescribing information from general practice databases. Time-trend analyses of the levels of usage and the characteristics of users would provide valuable insights into the extent to which safety messages are impacting on prescribers. It is important to recognize that general practice databases do not cover medicines prescribed in hospital or bought over-the-counter, and there is a need to develop usable and comprehensive information sources for medicines used in these environments.

True outcome measures would provide estimates of the impact of interventions on morbidity and mortality. Ideally, we would wish to be able to estimate how many deaths and serious adverse reactions are prevented by the whole pharmacovigilance system, as well as being able to quantify the effects of individual interventions. In terms of mortality, for some it seems unlikely that death certificates in which ADRs are mentioned as a cause would currently be useful for either purpose because of substantial under-recording. It is possible that this could be improved, e.g. by adding an additional field on the certificate to indicate that an ADR may have caused or contributed to death. Also, for some conditions, where ADRs contribute a substantial attributable fraction (e.g. gastrointestinal bleeding), then surveillance of mortality data could be helpful. For morbidity, in the UK, hospital episode (HES) data are a potential source, but they are of variable quality and likely to have important limitations, again because ADRs will not necessarily be recorded as a diagnosis on discharge. In the case of both death certificates and HES data, there would be a need to develop links to data on use of medicines and other health records.

Whilst the above potential data sources are worthy of further exploration, general practice databases are a more likely and immediately available source of data. Their potential should be evaluated in pilot studies of specific ADRs with high morbidity and/or mortality. For certain ADRs (e.g. major hepatotoxicity) it may be possible and more fruitful to obtain information from specialist referral centres and the advantages and disadvantages of these approaches could be compared.

In terms of the outcome measures themselves, we suggest that *years of life lost* should be the principal mortality outcome, since it is more informative than a simple mortality rate and can be easily calculated, providing age is known. In order to include morbidity and the impact on quality of life, estimation of *quality adjusted years of life lost* should be the goal, but this is likely to be much harder to measure. There is a need to evaluate the potential of the data sources discussed above to provide reliable data on these outcomes.

Audit

Audit is essentially a process of checking what has happened, usually against prior predictions, targets or standards. Currently, most audit in the field of pharmacovigilance is focused on data handling and quality, and is process- rather than outcome-orientated. Audit of effectiveness of literature scanning and the time taken to implement safety warnings after initial signal detection are particular examples of audit that could be done fairly easily, but they are not routine, or even if done they are not published. Broadly, there is a need to define

standards, extend audit across the whole process and focus particularly on whether the desired outcome was achieved using the measures discussed above.

In order to define the standards for audit for each party involved in the process there is a need for an internationally agreed document defining 'good pharmacovigilance practice'. Excellence in pharmacovigilance will require audit of the overall outcome using the types of measure discussed above and of each stage of the process, as follows:

- data collection and processing
- extending knowledge of safety
- hazard management
 - signal detection
 - signal evaluation
 - decision making
 - taking action
- Communication of safety and risk–benefit.

Effective use of resources and timeliness are important factors to be audited. Whilst the majority of audit can be carried out internally (preferably within a defined group responsible for this function alone), periodic external audit should also be a feature.

In order to develop the necessary methodology, there is a need to work retrospectively through some major issues to examine each element of the process and to question whether the best possible outcome has been achieved. Other possible approaches that are worth exploring include:

- Feeding in some 'dummy' data and measuring whether the response meets expectations.
- Testing reproducibility (e.g. by taking the same assessment to two expert committees).
- Making comparisons with others addressing the same issues (e.g. internationally), exploring reasons for differences.
- Considering the scope for 'trials' (e.g. prospectively comparing different courses of action).

Ultimately, the aim should be to develop a scheme by which audit of the whole process can be carried out, both on a routine basis and with defined triggers for additional activities. The development process should involve personnel with expertise in audit generally. The possibility of international collaboration in conducting audit could also be examined.

Culture of scientific development

This part of the model is about creating an environment whereby the pharmacovigilance function keeps pace with developing science and makes full use of the opportunities it

provides for preventing ADRs. This must not be dependent on individuals, but be an intrinsic part of the operation. The rapidly developing field of pharmacogenetics is the most important current opportunity, with many ongoing studies of the genetic contributions to differential drug response. It is imperative that these developments are translated into public health gain, but this will only happen if pharmacovigilance personnel gain expertise in the field and develop clear strategies to take advantage of them. There is also a need to adapt the pharmacovigilance process effectively to take account of different types of new therapy being developed (e.g. gene therapy) and which are likely to require specialized monitoring in a tertiary care setting. Again, this requires a culture of scientific development in order to facilitate the necessary work.

Information management is also relevant to this aspect of the model. Effective use of information to create a knowledge base, which underpins the scientific functioning and is not dependent on individuals, is also a prerequisite for a culture of scientific development.

Scientific basis of pharmacovigilance

Pharmacovigilance is a preventive public health function underpinned by several scientific disciplines. The key disciplines may be grouped into four broad areas as follows:

- basic science
- clinical science
- population science
- information science.

These disciplines can be related most clearly to the best evidence part of the model, but they also impact on all the other elements. Since there is a need to change clinical practice, it can be argued that behavioural science should also be included. It is important that there is a good balance of resources and expertise between these disciplines. It can be argued that, at present, the balance of inputs may not be right and that there is a need to increase the input of basic and population sciences.

At present, there are few dedicated academic bases for pharmacovigilance in most of the world. This needs to be rectified in order to underpin a culture of scientific development for pharmacovigilance and support training programmes. Dedicated academic departments of pharmacovigilance would, in particular, require close alliances with both clinical pharmacology/therapeutics and public health/epidemiology.

Basic training

Most recruits to pharmacovigilance, whether in the regulatory authority or in industry, have little or no specific basic training in the field and, therefore, this has to be done 'on the job'. In practice, this means that too high a proportion of time is spent in basic training whilst in post, when the focus should be on further development and specialization linked to a career development pathway. Although there are a few courses that concentrate on pharmacovigilance there is a need for specific basic training courses in the field. These need to be focused

on the preventive and public health functions of pharmacovigilance and not solely on regulatory requirements.

Organizational aspects

The nature of pharmacovigilance is that the casework is completely unpredictable and there is more to do than can ever be done. Each case is unique, and major issues are difficult to handle, requiring a high degree of involvement from experienced personnel. The inevitable consequence of this is that progress in strategy and development is hampered and the only realistic way to counter this is by dedicating protected resource to these areas.

Conclusions

A scientific model to support excellence in pharmacovigilance is proposed. The model represents a long-term vision of how pharmacovigilance could be conducted in the future. So far, it has been developed without considering constraints such as resources or the need for legislative change. Although the vision is holistic, it would be possible to test and implement parts of the model in a piecemeal fashion.

The key concepts underpinning the model are as follows:

- Pharmacovigilance should be less focused on finding harm and more on extending knowledge of safety.
- There should be a clear starting point or ‘specification’ of what is already known at the time of licensing a medicine and what is required to extend safety knowledge post-authorization.
- Complex risk–benefit decisions are amenable to, and likely to be improved by, the use of formal decision analysis.
- A new approach to provision of safety information which allows greater flexibility in presenting key messages based on multiple levels of information with access determined by user requirements.
- Flexible decision support is the most likely means of changing the behaviour of health professionals in order to promote safer use of medicines.
- There is a need to put in place outcome measures that indicate the success or failure of the process. These should include hard end-points indicating the impact on mortality and morbidity. Surrogates, such as the impact on prescribing of medicines, are more readily available and are also potentially valuable.
- Systematic audit of pharmacovigilance processes and outcomes should be developed and implemented based on agreed standards (‘good pharmacovigilance practice’).
- Pharmacovigilance should operate in a culture of scientific development. This requires

the right balance of inputs from various disciplines, a stronger academic base, greater availability of basic training and resource that is dedicated to scientific strategy.

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