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REVIEW ARTICLE

The future of pharmacovigilance: a personal view

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History

Modern drug safety, in the sense of widespread, routine, post-marketing surveillance of drugs for new safety issues came into place following the unpredicted teratogenic outcomes from the use of thalidomide in the mid-1960s. To provide a regularized tool for medical practitioners to report suspicions of possibly drug related adverse events was thought to be a sensible and practical catch-all for drug related problems. Then, and now, it was only one possible mechanism to review the safety of drugs in clinical practice, but reporting of individual case safety reports (ICSRs) has set the scene for sending information relating to the real life use of drugs. Initially, ICSRs were assessed for the possible causal relationship to a drug, singly and in clusters, by clinically trained pharmacologists, and databases around the world were populated with assessed reports.

By the 1980s, there were so many ICSRs sent in to the national agencies in heavily populated countries, particularly in the USA, that clinical assessment of individual reports on input became impractical, and a public health approach was adopted: pharmacoepidemiology was born. This change was highly significant. Looked at from an epidemiological aspect, ICSRs are sometimes poor material to prove a relationship between a drug and an adverse event. Reporter bias, drug use factors, lack of quantification of numerator and denominator are a few of the drawbacks. Since then, epidemiological methods have held sway, particularly in the USA, where it was also possible to use large health care databases to perform observational studies. Thereafter, very little was heard of the careful clinical and pharmacological assessment of ICSRs, and the development of hypotheses.

Some countries, France for example, went a different way to manage the challenge of increasing numbers of reports, and set about developing strong regional centers using agreed methodologies to assess ICSRs, before pooling them in their national database [1, 2]. Those centers have also been very much involved in clinical management and advice of drug related injuries, thus creating a strong position of healthy dialogue with reporters.

Most other countries have made progress between these two extremes, and now the collection and evaluation of ICSRs and also observational and large interventional studies are used to a greater or lesser extent in all 83 countries of the WHO Programme for International Drug Monitoring.

So can we say progress has been made towards the goal of safer use of medicines for patients? I will argue that the answer is doubtful. The doubt is based on several critical matters that have not been resolved.

- Complete safety is not achievable with therapies: there will always be some harm from medicines. Our use of the term is relative, but there is no agreement as to what is a satisfactory level of safety, compared with what, from what perspective, agreed by whom, and measured how.
- Drugs on the market change continuously, their use varies over time and geographically. Approaches to the consideration of safety are subject to scientific, political, and legal influences, which change.

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- Audit of pharmacovigilance activities in public health terms is primitive; often measured in the number of drug withdrawals or warnings issued.
- Various players in the pharmacovigilance arena take circumscribed and ill-coordinated, even adversarial positions.
  - There is a total break in responsibility between regulators and industry, which provide information on medicines and make them available, and those who prescribe medicines. In several studies, about half of serious adverse reactions have been said to be 'avoidable' [3, 4]. This suggests a serious defect.
  - There seems to be more interest in pharmacovigilance methodology than in transparent, cooperative, peer reviewed, logically consistent decision making.

For these, and for some lesser reasons, I hold that the somewhat fruitless public debates about drug 'scares', expensive litigation, and huge expenses on pharmacovigilance are destined to continue without real progress being made.

But first, I would like to emphasize one peculiarity: drug products are not quite like any other products by virtue of the heavy dependence on a 'learned intermediary' for the prescription and dispensing of the product between the manufacturer and the public users of the product, at least in countries with heavily regulated health care. In fact, in those countries it is not one, but up to four such intermediary entities, the prescriber/dispenser, the health care maintenance authority (which issues general management plans for patients), and the regulatory authority (which decides on restrictions and availability of individual products). Each of these 'learned intermediaries' makes decisions about benefit and risk from medicines, and in none of the decisions is there complete transparency for the end user. Moreover, the interests and responsibilities of each intermediary may be in conflict at times, as mentioned above. For no other range of products is the technical complexity so great, the breadth of use universal, the impact so personal, and the responsibility for successful use so dispersed.

Current challenges

A close look at the current situation reveals the following main matters for concern:

- The public continues to lack confidence in either regulators or industry over the public perception of provision of 'safe' products [5]. Much of the concern relates to lack of timely information to the public. The pharmaceutical industry has a particularly problematic status in the public's perception, which needs to be clarified, and probably changed [6].
- Drug regulation, including safety monitoring, continues to be carried out primarily between regulatory authorities and the pharmaceutical industry. There is provision for 'confidential' external expert advice, but, except in the USA, there is very little continuous, comprehensive, external, public, audit. Many in the public believe that decisions are made for political rather than public health reasons and that industry's commercial goals heavily influence decisions on the registration and safety monitoring of drug products. Such negative feelings are widespread, even though it is clear that there must be political influence to ensure reasonable equity of health care in society. The matter is particularly sensitive with drug safety matters since it is easy to blame regulatory or company decisions for 'unsafe' products: this is particularly true when information is regarded as 'commercially confidential' even though it relates to safety. Moreover, the evidence basis for safety decisions and safety issues under consideration are not made public, since much of the data is considered 'commercially confidential'.
- There is no audit of the performance of regulatory or industry performance in reducing the risk of drug therapy, in spite of reports indicating that iatrogenic disease is amongst the highest, if not the top five [3, 4, 7], causes of morbidity and mortality in the western world. About half the iatrogenic disease is assessed to be avoidable, and the cost to health care services great. In the developing world, the cost of iatrogenic disease may be decreased due to the lack of availability of pharmaceutical products, but will be increased by lack of health care professional supervision and fraudulent and substandard drugs. The way in which decisions are made about drug safety signals and the decisions about specific drug safety problems and their analysis is not open. Which signals are under review by regulators and industry, which signals have been rejected, and which are actively under analysis by various methods is secret information. The health care professions, let alone the public, have no idea or involvement in the safety work being undertaken on their behalf.
- The increasingly complex medical, and particularly therapeutic work, which health professionals undertake is performed under increasing scrutiny by the public and also by managers who require increasing efficiencies. Information about the effectiveness and risks of drug products (let alone other therapeutic possibilities) is only accessible piecemeal. The main authoritative information is in the summaries of product characteristics (package inserts, SPC); this information is difficult to use, much abridged and can change without there being

obvious warnings of such change. Moreover, comparative information on therapeutic options is not easy to find, although the Swedish Medicinal Products Agency and the UK's National Institute for Clinical Excellence (NICE) are examples of authorities that perform such work, although limited by resources. Furthermore, for many years, the WHO has done similar work in its Essential Drugs Program, which now uses a strongly evidence based approach to recommending drugs of proven clinical value. The current pressures of cost effectiveness in health care delivery and the limited information on effectiveness and risk of drug products are contrary dynamics which inevitably lead to suboptimal and even unsafe therapy. The high cost (morbidity, mortality, and financial) of iatrogenic disease has been repeatedly shown, but attracts very little support for its reduction. New thinking is needed to improve therapeutics, but this must be a general move to support those involved in day-to-day clinical care. Currently, I see much that pressures clinicians away from taking thought on therapeutic decisions and following up for effectiveness: piecemeal treatment by several clinicians is just one challenge, when no one coordinates the therapies.

- The methodology of gathering and analyzing safety information is under continuous and often acrimonious debate. Unlike decisions on drug safety and drug regulatory issues, much of the work other than gathering ICSRs, is carried out by independent groups, often academics. There is no, or little, independent funding for drug safety analytical work, mainly that provided by the pharmaceutical industry. Awareness of this heightens public concerns over safety matters being suppressed because of industry self-interest.
- Through the activities of the International Conference on Harmonisation (ICH), there is now a standard way of transmitting ICSR information. This has also resulted in even larger amounts of ICSR information being shared in databases and via Periodic Safety Update Reports (PSURs). As a result, there is much duplication. There are timelines for reporting of, particularly, serious ICSRs, but there are no guidelines for the data quality of the reports, and little assessment of the likely causality of the reported event(s) by the drug(s). It is fair to say that the percentage of useful reports in the global data reduces by the year, certainly not altered by the introduction of the ICH E2B format. The key fields used for causality assessment have shown some decline [8]. In a sample of every ten reports in the WHO database in 2000, the percentage of reports with dates (specified to month and year) for onset of reaction was 82% and the treatment dates 41%: by 2005 the figures were 68 and 44%, respectively. Both these fields together are essential to even the most basic of assessments of causality. There are many duplications (a definite 1.8% in the WHO database, with more than 30% unevaluable because of lack of data on the reports [9]) In addition, I have observed many spurious adverse reaction terms being included in ICSRs, as adverse reactions where, for example, further investigation shows that the term was the indication for use of the drug.
- Much effort is made to ensure that ICSRs are delivered in a timely fashion to regulators, and as stated above, this data of decreasing quality but increasing amount is what most regard as the primary way of detecting early signals that new drug related problems are emerging.
- Whilst ICSRs continue to be the major way of generating hypotheses of new drug-related signals, the volume of data has led to the introduction of data mining methods to find potentially important associations from huge amounts of data [8, 10, 11]. On the other hand, there much concern that data mining will find more spurious signals, thus creating unnecessary noise in safety systems, or worse, drug scares in the public domain
- Observational studies are the most frequently used method of hypothesis confirmation of the relatively rare post-marketing adverse drug reactions, although they are criticized for bias and confounding, as well as the limitation of showing only relative risks. Larger numbers of longitudinal data bases makes such studies easier to do, but inadequate numbers of exposed patients is still a challenge given the levels of risk which we currently believe we should encompass.
- Large scale, controlled prospective cohort studies are seen as the desired standard for specific epidemiological answer to safety matters, but they are interventional (interfering with normal clinical practice, and selecting patients) and expensive. Moreover, from the time of a signal /hypothesis to answering the question from a cohort is considerable.
- Both observational and prospective cohort studies are much supported by academics and industry as more useful than ICSRs because of their greater specificity and objectivity but they have had limited value in the recognition of signals because they need a specific hypothesis for their best use. General hypotheses much reduce their specificity and their value. They are untested as overall safety surveillance methods, although data mining of large health care data bases, such as the WHO Collaborating Centre for International Drug Monitoring and IMS Health have piloted may have considerable value in finding new signals of different types of drug related problems.
- Responsibility for the availability of safe and effective drugs is shared between regulators and industry. Legal actions are frequently taken against the pharmaceutical

industry in spite of regulators being fully complicit in the decisions taken.
- For developing countries, the challenges in all areas are magnified due to scarce resources. Not only are there a limited amount of drugs but the distribution is problematic and monitoring of their use less because they may be obtained often without prescription or professional dispensing. Also, counterfeit and substandard drug products are more difficult to detect. The introduction of new products to these countries may also unexpectedly cause adverse effects because of the different genetic make-up of the population or the disease burden (such as malnutrition). The overall result is likely to more drug-related injury to further burden health care. It is also likely that a greater proportion of the important safety signals may reflect the way that drugs are used, or the setting in which they are used, rather than being directly caused by the drug. The management of HIV/AIDS provides an excellent example of all the above challenges.

The way forward

We could be on the edge of significant development in pharmacovigilance. There are three major moves that bode well. They are:

- the concept of risk management commencing at the start of drug development and continuing throughout its life
- the development of patient safety as a discipline and a major preoccupation of healthcare
- and the potential for IT to revolutionize communication in health care, both in developed and developing countries.

There are also many other important matters which need special attention, not being considered currently, which I shall consider below.

Risk management

That every drug should have continuous lifetime management seems obvious, but its achievement has been elusive. This has been largely because, bureaucratically and logistically, drug development has been seen as discontinuous steps managed by disparate professionals. This has been reinforced by regulatory processes over the years. We now have a renaissance view of chemicals in society. We need to know what any synthetic substance might do to humans, animals, and the general ecology. Nothing short of that is satisfactory for the future.

Risk management should start with an evaluation of the molecular characteristics of a new product, comparing them to extant chemicals and our knowledge of their properties. There are already powerful graphical and molecular conformation analytical tools which allow such comparisons to be performed quickly. They are used in drug discovery, but there is less use of them for risk prediction. Clearly pharmacological, toxicological and early human studies will all add information on risk. Such risk management is starting, but two issues deserve emphasis for the future: one is the impact of drugs and metabolites on the environment; the second are the long term possibilities of drugs, particularly biologicals and genetic manipulations, to result in profound, late, permanent changes in the body.

Overall risk management needs audit. There must be active surveillance of the effectiveness of risk prediction and management activity to ensure that it results, optimally, in the desired end of reducing risk, in a measurable way. It is salutary to note that we have not been very active, certainly not consistently, in checking that new adverse reactions seen first in the post-marketing period could not have been predicted pre-marketing. It is important to comment here on the much quoted ‘precautionary principle’. Many seem to interpret this as, “If there is any conceivable risk, don’t do it.” This certainly will lead to the stifling of research and development, and it is not the aim of pharmacovigilance. The better interpretation is that risks should be identified and *fully* understood as quickly as possible and constantly evaluated against expected, and actual, benefits. Moreover, there should be open, continuing and clear information and dialogue at the right level, on the expected benefits and likely risks at a general and individual patient level. In therapeutics, risk is always there, and it is important that patients understand the potential benefits and risks as far as they are able. This can only be really achieved if the public as a whole accept the principles of benefit and risk balance. This is an important educational task. There is another angle to the precautionary principle for pharmacovigilance, however, and that is not to too easily dismiss the possibility of drug causation of an adverse event when dealing with limited evidence. Too often case reports and study results are put down to confounding when such a conclusion is not justified by any solid evidence either. We should not fall into the trap of giving the benefit of any doubt to the drug, if anything, it must always be given to patients.

Patient safety

Drug safety has increasingly been regarded as an epidemiological or ‘public health’ exercise. Most adverse reactions to drugs are relatively uncommon and they more usually result from individual patient idiosyncracy or from the way

in which the drug is used, perhaps by medical staff or the patient. Sometimes it is not the active drug substance causing a problem, but may be an excipient, a poor formulation, or even a fraudulent product. A concentration on individual patient safety and medication error is very much allied to the analysis of ICSR [12]. It has been demonstrated repeatedly that about half of the adverse reactions to drugs are avoidable, and it should be clear that careful analysis of individual cases is the best way to determine all the factors that have contributed to a single patient's problems. This is not the purview of epidemiology which is primarily concerned with the generality or norm in a population. Pharmacoepidemiology is the correct public health tool for determining whether the overall effectiveness to risk balance for a drug is satisfactory for overall use to manage the generality of patients: it is not the best way to decide whether adverse reactions may occur in a small number of situations. This is not to say that epidemiology has no place, but it is a small one given that the data one needs to identify all the causative factors for a particular clinical outcome maybe complex, and certainly not normally included in any epidemiological hypothesis for investigation of rare events, where the usual aim is simplicity.

On the other hand, much useful individual information is available on patients which are included in studies. We should start to look at that information more closely, indeed it should be mandatory to include a review of the characteristics of all study patients, included in the study or rejected, for individual de-challenge information, doses, co-morbidity, co-prescription, and much more (see below). This information might be useful in addition to the evaluation of the main hypothesis.

Patient safety analysis uses approaches gained from other areas where safety is a concern such as the chemical and transport industries. In terms of risk management, these industries use methods such as 'fault tree analysis' for the prediction of risk and 'root cause analysis' for the evaluation of incident. Such methods are not dissimilar to the more familiar medical diagnostic approach which sets out the patient's clinical problems in an integrative and prioritized way. The main differences in applying such an approach to medication error and adverse events in general are a fuller description, and analysis, of factors extraneous to the patient. There is also a need to report situations where things nearly went wrong. A pilot project is under way under the joint auspices of the WHO Programme for International Drug Monitoring and the WHO Alliance for Patient Safety, to find out how drug monitoring centers could extend their roles, particularly the scope of information on ICSRs to include more detail of the avoidable background to adverse reactions.

Patient safety is also much in the scientific gaze in relation to pharmacogenetics. Aside from medical error (including known interactions) and disease effects, many adverse reactions are an expression of an unusual human phenotype, in that those adverse reactions are not due to external factors and occur in a minority of the population. There are several proposed initiatives to look at this. The challenge is great since, being rare, a large population of phenotypes is necessary to investigate the genomics of adverse drug reactions. The WHO global database of ICSRs offers potential in this regard, if the logistics of data and sample collection can be overcome. Near-patient testing and technical advances in genotyping make the possibility of predicting adverse reactions to medicines feasible, although such an approach is in its infancy.

Information technology and data management

Patient therapy is an increasingly complex exercise. In spite of, or perhaps because of, the information explosion, a practicing health professional, faced with the special needs of a patient, is often ill equipped with reliable, up-to date information about the optimal treatment. The real paradox is that there is a huge amount of information available on the web for those with the time to search for it and analyze it: patients do this all the time. The challenge is to collate it, establish its veracity and evaluate it in context while the patient waits for an answer. There are many efforts to try to provide 'near-patient information', and indeed to manage patient clinical information so that it is available to those who have a need and a right to access it. In spite of the efforts to provide such systems, workable solutions to really useful data provision and management for patients care remain woefully short of what is needed to support patient care which operates on much too limited consultation times and which seems to have a concentration on supporting bureaucratic needs rather than clinical. The realities are that, so long as IT systems are intrusive in consultation times rather than being supportive, they will not be used optimally. I have been able to observe several such systems being use, have first hand experience of their limitations and the resultant failure of health professionals to use them optimally. To give just one simple recent example of IT planning failure, a hospital created an internal IT network that was not immediately compatible with the primary care system in use locally, making coordinated patient management difficult.

For pharmacovigilance, health professionals need much more support and information than is available in SPCs in order to avoid, diagnose and manage the relatively rare adverse events that result from drugs. Much useful information is available, but not as a single, authoritative site. We need to be able to access reliable information that allows us to compare the effectiveness and risk profiles of treatment options readily. The information displayed must

be up-to-date, comprehensive both with fact and opinion. Such a high requirement was outlined in the Erice Declaration [13] and reaffirmed in the Erice Manifesto [14], but the implementation has proved elusive. This is because there is fragmentation in approach to this challenge. The Cochrane Collaboration has done much to assemble proven clinical trial information on specified areas, but it is not comprehensive, excluding other information such as ICSRs. This may change for the better now that a new Cochrane group to look at the issue is assembled. The National Institute for Clinical Excellence (NICE) has also done splendid work in providing therapeutic guidance, taking into account efficacy, safety and cost. These are two good examples of work along the right lines, and there are many more, but it is not easy for a busy health professional to access all of these in an easy way when required. The Heath on the Net Foundation (www.hon.ch) does provide some model for what could be the way forward in giving access to a variety of sites for information that reach set standards. Their site does provide easy access to scientific information (such as MEDLINE) as well as information from meetings and discussion groups. Is it not possible to add to such a website the frequently asked questions and for a professional group to provide guidance over FAQs? Or is it that we are overwhelmed by the legal problems that might ensue from such an approach?

Overall, it is clear that the safety matters relating to drugs are not usually put into context with effectiveness (or cost) except in some studies which one needs considerable time to find either via MEDLINE or Google.

Further changes needed and obstacles to progress

A holistic viewpoint

Most recognize that the safety of a medicinal product cannot be divorced from a consideration of its effectiveness, nor its potential for use and misuse in clinical practice, and in comparison to competitor products. In spite of this, the pharmaceutical industry and regulators seem to behave as if there were separate compartments. ‘Seem’ is used advisedly because it is clear that many pharmacovigilance professionals in those areas are only too aware of this. However, it remains that segmentation of responsibility seems to lead to many problems in the evaluation of drugs. One aspect is absolutely clear; there is virtually no unbiased consideration of how to improve the use of drugs in clinical practice by those who have access to the greatest amount of information and resources. The overwhelmingly common view is that once information is provided in an SPC, the responsibility of industry and regulators is fulfilled; it is the responsibility of others, often at a local level to interpret the often limited information, and to work out effectiveness and risk as well as cost of competing drug products. This could work if there were to be a much more effective network of experts involved, with a detailed examination of patient and healthcare needs, and active iteration of knowledge based on frequently asked questions. The essence should be for regulatory authorities to create an open, active, responsive process which involves feedback from health professionals and patients as well as industry: A more active use of expanded ICSRs, as expressions of concerns about the safety of products, would be one way of doing this, and patient safety relating to drug use matters should be included. Such a vision is not unrealistic in developed countries, where it is common for there to be product complaint departments in other industries.

Interestingly, experience in developing countries shows that regulatory and pharmacovigilance centers are already much more involved in reacting to a broad spectrum of drug safety and therapeutic problems in the community. One example is the identification of therapeutic failure due to the use of fraudulent products; another is the detection of problems relating to ‘off-label’ use of drugs. In developing countries, there is a much closer link between pharmacovigilance, poison control, and drug information. This is due, in part, to the limitation of human and other resources, but it has the positive value of a much broader view of drug safety matters and of reactivity to the whole community.

Pharmacovigilance science

The most elusive factor in improving therapeutics is our inability to relate effectiveness to risk in clinical practice and thus compare drug products. Efficacy data are quite useful in predicting effectiveness in clinical practice, although it must be said that complex factors involved, such as interactions with other drugs or concomitant disease, seem often to be overlooked by health professionals in their prescribing. It is certainly doubtful if the average clinician knows enough about drug interactions other than to avoid such combinations. Information about the quantitative aspects of interactions and their clinical relevance is scanty.

On the risk side, qualitative information is limited and quantitative information very patchy. Apart from common adverse reactions, we rely still mostly on uncontrolled information or on observational studies. We therefore have considerable difficulty in comparing the likely effectiveness and risks of a drug: the efficacy is well defined, quantified but not reflective of real-life use, and the risks are multiple, much rarer, and poorly quantified.

In the IT industry, the purchase of equipment often involves technical knowledge, which is not possessed by the potential user, just as in medicine. Most of us buy computers and mobile phones based on expert reviews in a

multitude of journals. There is very little available to compare drugs that is similar to those consumer comparisons, although the journal 'La Prescrire' has elements of the right approach. Risk benefit (or effectiveness to risk) assessment needs to be developed to a point where it is possible to compare drugs in a given indication much more easily than at present. A significant challenge is the collation of different kinds of safety information: variable study information and ICSRs. Variation in quality and import of information needs to be handled transparently and not by exclusion. More than anything, we need semi-quantitative ways in which we can compare the benefits and risks of competing drugs. Unlike other areas, such as IT and electronics, we do not have many available publications, used by every professional as well as the public, which describes the 'best buys' for drugs and certainly not laying out their characteristics in easy comparison tables. Why is it that the pharmaceutical industry does not publish the data on their product that was used to register them? Everyone can read the performance characteristics of a car and a computer: why not a drug?

It is also interesting to contemplate why the few websites and journals that attempt drug comparisons are not read as avidly by healthcare professionals as the corresponding professional journals are by IT experts.

Legal liability

There is little doubt that concern over litigation affects the way effectiveness and risk about drugs is viewed. The logic system used in legal review is essentially case based and there is a need for the science and information used in a case to be explicable to lawyers and 'the reasonable person'. Moreover, the legal adversarial process examines the validity of expert testimony and requires decisiveness over probabilistic information relating to a specific case. A common viewpoint is, 'Would a reasonable doctor have treated a patient in this way?' Much argument then arises over what information should that 'reasonable doctor' be expected to know.

As far as a pharmaceutical company is concerned, they have a duty to warn in the case of risk, but they also have a duty not to over-warn—to cover up serious information by immersing it minutiae [15]. In spite of this many claims are made against the pharmaceutical for 'failure to warn'. Manufacturers also operate under strict liability, that is, negligence need not be proved when personal injury is caused by their products, for which the producer has issued no warning or instruction for use. Some say strict liability operates as a kind of insurance system: since the manufacture is free to increase prices to cover litigation for damage, ultimately society pays for those who go to litigation for injuries proven to be due to a product.

A number of points arise from this. The interpretation of clinical trial and epidemiological information by a doctor, or effectiveness and risk as relating to a particular case or cases, is not straightforward. What level of probability is 'reasonable'? The outcome of a debate in court on such a matter may not be easy to predict, and leads to many settlements out of court since the industry may feel that this is the cheaper option than a defense, even though they may have a case, perhaps based on getting better evidence for harm than a series of ICSRs, for example.

More important to pharmacovigilance, however, is the duty to warn. Most seem to interpret this as the need to list an adverse effect which might reasonably be related to a drug in the SPC. Since the SPC is agreed between industry and regulators as well as lawyers as a legal document, the wording used is carefully chosen to fulfill legal requirements with strict liability warnings in mind, rather than as a communication document for the average person. There is a conflict between such careful, defensive wording and content versus the provision of full, useful information for health professionals and patients. This is certainly not the intent, but it is the result of anticipating what may happen if there is litigation: one should say just enough to state a risk exists, but no more, no fodder for litigants!

The interplay between science and legal requirements, and the degree of responsibility of health professionals to interpret information (and even over-ride) recommendations from the manufacturer in treating patients, is complex. This is particularly true in the presentation of risk to benefit information and the separation of degrees of certainty of data and opinion in the area of evolving risk situations.

Medical practice

The high level of avoidable adverse drug induced adverse events in clinical practice not only argues for better information systems and technology, but also for other improvements in health professional practice. Short consultation times and other non-clinical pressures reduce the time spent on all-important therapeutic decisions. The pressures put on health professionals for increases in time efficiency are not conducive to the essential, and variable, time to relate to patients and communicate complex messages to them about their medical condition and its treatment. There is no incentive at all to follow up patients to see if the treatment is effective, unless it is particularly complex such as in anticoagulation or cancer chemotherapy. It is worth noting that anti-retroviral treatments are used in developing countries with very limited monitoring. I wonder whether there is good information in those countries on the development of resistant HIV.

There is also a lack of time in learning good therapeutic practice in medical education as well. The time spent in

pharmacology and therapeutics is less and less in spite of its increasing complexity and obvious importance in getting the best results on morbidity and mortality. There is a trivialization of the therapeutic act compared with other areas of medical competence. Neither before nor after graduation is there much encouragement to follow up the outcome of therapeutic decisions in a consistent and logical way to ensure that the result is optimal for the patient. Unless health professionals can practice in a reasonable way, the high levels of medical error will persist.

Conclusions

There is a fundamental need to define what risks patients are prepared to take and in what circumstances. The days when a benign, paternalistic, governmental, industry, or professional group can decide such matters are gone. Patients must be fully involved, both in decisions and information about drug benefits and risks as well as listening and acting upon their feedback (via ICSRs).

There is an urgent need to reconsider the relationship between the pharmaceutical industry, health professions, regulators and the legislature over how damages from medicinal products can be best avoided and, when they occur, as they inevitably will, are handled.

A new holistic view is essential on warnings and the availability of products, and how more useful information can be best be presented to all drug users, professional and public.

There is a great opportunity for progress afforded by the new risk management thinking, and extending pharmacovigilance's gaze on all the factors which cause harm from drugs, not just those intrinsic to the drug itself. Pre-marketing risk identification and the subsequent development of risk management plans should allow for a much better consideration of the comparative risks of products for the same indication. It should be possible to see how the efficacy-risk profile of a new drug compares with those already on the market, and to determine where more information might be needed on the new drug to determine its relative place in therapy. It would then be possible to create a no-fault compensation fund into which companies would pay according to the public health value and safety profiles of each product. As knowledge of the product develops the tariff paid could change accordingly. Such an approach would have the following benefits:

- Drug regulatory agencies would focus on the way in which, particularly new products, are likely to impact on the effectiveness and safety of treatments for an indication. The 'product' would be not only the active ingredient and excipients, but incorporate all the strategies and communication proposed for its safe use. The gaze of drug regulation would move from checking that industry was providing complete and accurate information on their product and evaluating it at registration for marketing authorization, to a concentration on how the producer will ensure the value of their product relative to others whilst on the market in a much more dynamic way. Companies would also need to prove the effectiveness of their strategies to maximize effectiveness and reduce risk to public health. Those strategies would include appropriate promotion and oversight of appropriateness of the use of their drugs, as well as withdrawal of irrational medicines especially in less developed countries.
- The compensation paid for drug induced injury should be only for real need due to ongoing disability, but would include patients damaged by medical misadventure: a no-fault compensation scheme. Medical negligence in failing to follow adequate guidelines, without justification, in an individual case would be subject to medical professional disciplinary action. Failures by the company in risk planning and performance would be dealt with by greater subsequent payment into the compensation scheme. This would protect companies from litigation under strict liability and partially from negligence claims. There would need to be a consideration of how such a scheme could be introduced into current legal frameworks, as well as an analysis of the economics.
- If there was actual negligence within the company leading to the failure in risk planning, it might still be dealt with according to the usual legal structures, although most serious accusations against companies concern withholding information, which might be managed by legal searches.
- The scheme would encourage pharmaceutical innovation, since 'me too' products would carry a high compensation tariff because of their relative failure to contribute to public health. New, potentially valuable products with adequate risk management planning would attract lower tariffs.
- There would be a progressive improvement in the way benefit and risk comparisons between products are made since that information would be the key to commercial success and lower tariffs into the compensation scheme. This will alter the dynamic of stewardship of the pharmaceutical industry away from passing a single regulatory hurdle towards the development of good science showing real benefits, and reduced harm, to patients throughout the life of the product. This will not only improve the pharmaceutical industries' impact on public health but enable them to enhance their public image [6].
- The future of pharmacovigilance will be improved by scientific developments such as genomics, informatics and communication, data mining, and outcomes re-

search. These and other innovative methodologies, however, can only produce results for patients in a changed setting where patient safety is considered in a holistic way by those who have influence over it in prevention, or in the management and consequences of any harm which may always result from therapeutics however much care is taken.

- All of the benefits mentioned must be considered in relationship to developing countries. It is naive to think that the delivery of medicines to those countries, and their distribution, will be successful without their monitored use: patient safety issues are paramount. The intermittent use of anti-infective agents in diseases such as tuberculosis, malaria, and AIDS is likely to result in resistance. The adverse effects of drugs used in these three diseases need careful management during their use.
- Pharmacovigilance should assert, as its vision, the full monitoring of drugs and their use in clinical practice, together with interventions to ensure their best effectiveness with least risk for the public and individuals. Key components of pharmacovigilance should be effective communication to alter behavior positively, audit of the outcomes and iteration to produce the best final standard.
- An essential development is the need to ensure that those who suffer in a major way from the adverse effects of drugs, or from drug-related medical error, can be compensated without expensive litigation. The pharmaceutical industry should pay most, if not all, the compensation as they do now, but as an annual fee for continued registration. They should be able to benefit from good risk management planning and high positive pubic health impact of their products by paying less into the compensation scheme and avoiding almost all current lawsuits.

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