LEADING ARTICLE

Drug Safety 2004; 27 (8): 609-617
0114-5916/04/0008-0609/$31.00/0

Managing the Interface with Marketing to Improve Delivery of Pharmacovigilance Within the Pharmaceutical Industry

Brian Edwards

PAREXEL International, Uxbridge, United Kingdom

Abstract

The pharmaceutical industry is under pressure to improve the scientific quality of its decisions concerning the benefit and risks of its products while ensuring compliance with acceptable standards of marketing. All those in a pharmaceutical company who currently work within pharmacovigilance should be encouraged to lead from the front to examine ongoing marketing activities to see how they can be adapted more towards pharmacovigilance and risk management. The current irony is that the personnel who have the greatest influence on benefit-risk decisions of a product are not necessarily those who acknowledge that they are performing pharmacovigilance. Indeed, for all concerned, whether their orientation is scientific and commercial, effective communication with prescribers and consumers usually underpins product success. Also, a substantial 'marketing' budget is culturally acceptable for the pharmaceutical industry so it is logical to assume that resource for postmarketing activity is often made available. Given these realities, I suggest we should strive for an integrated marketing and risk-management plan based on the best available evidence and that being fully aware and in control of the safety issues for your products is the best way to commercialise them successfully. This approach can still be consistent with other corporate responsibilities such as trying to reduce the financial burden of product development. If this article stimulates further debate about how the pharmaceutical industry can more effectively organise resources and operations to support pharmacovigilance, risk management, and marketing, then it will have achieved its purpose.

1. Introduction and Rationale

One of the key challenges facing all those within the pharmaceutical industry whose remit is to develop pharmacovigilance and risk management (PRM), is how to successfully harness enough resource and expertise. A further challenge is how to address conflict with the commercial aims of a pharmaceutical company having to operate in a fiercely competitive environment. In reality, within most companies the main benefit-risk decision makers, on a day-to-day basis, are those with a marketing or commercial agenda. Thus, if we assume PRM is all about balancing risks and benefits and taking appropriate action, it is difficult to conceive how a company can adopt a voluntary approach to PRM without closer collaboration with marketing. The premise of this article is to suggest that one logical way of implementing voluntary PRM within a company is

to first examine pre-existing activities to see where closer collaboration might more effectively deliver results. Some companies, such as those who intend to develop more complex products where physicians and patients will need considerable support or those where staff are obliged to have multiple roles (such as for biological products and orphan drugs), may find it practical to take a more integrated approach to merging PRM and commercial objectives. However, for industry in general, marketing personnel should be encouraged to evolve a more pharmacovigilance way of thinking with the patient at the centre. There is no evidence as such to support whether one marketing activity is more appropriate than another for a PRM. Fortunately, those who work within PRM are accustomed to making the best of what they possess and know, however scientifically imperfect that may be. As benefit-risk decisions about products have to be made here and now, we cannot afford to simply wait until there is 'clear' evidence, but are obliged to try our best in finding ways to work more effectively within industry.

2. What Are the Goals of Ongoing Interactions Between Pharmacovigilance and Marketing?

Operational barriers between PRM and marketing personnel might be reflected in different goals and horizons as well as operating within different timeframes. Another approach which has been suggested to improve collaboration with marketing is to try and find common ground, such as: "we are all agreed that we do not want the product to be used when contraindicated," or "we are all agreed that we must work together to do our best not to make false and misleading statements about our products".

Common goals might be one method to improve the quality of evidence on which we base claims about the benefits and risk of our products and how we can better understand patient and prescriber behaviour to meet their needs in real life.[1] If a company were to reorganise, then I suggest that a medical department combine the medical services required for pharmacovigilance and medical marketing with a common mission statement, which might be drafted as follows: "To commercialise the products to their maximum potential whilst at all times acting in a medically ethical manner and fulfilling all regulatory requirements".

This statement is crafted to show that it is not possible to commercialise a product outside the bounds of ethical behaviour and regulatory compliance. In essence, any deviation beyond these boundaries ultimately will lead to exposure of the issues, a collapse in confidence in the product and potentially catastrophic consequences for the company. Put another way, this statement shows that being fully aware and in control of the safety issues for your products is the best way to commercialise them successfully. In the knowledge that guidance and oversight from pharmacovigilance is required for regulatory and scientific integrity, those in marketing should remain the owners of the activities, as they know best how to successfully implement them. Once a company has experienced one successful collaboration, then this is likely to lead to more long-lasting improvement in scientific relationship.

3. What Are the Hurdles to Interactions Between Pharmacovigilance and Marketing?

I think most people would agree that working relationships between pharmacovigilance and marketing are not always easy and are at times fraught. Operations and structures vary from company to company about how the marketing function is arranged such that sweeping comments are not helpful. However, barriers and misconceptions between the two company functions are inevitable and should be anticipated so that they can be tackled head on. The types of myths outside the traditional pharmacovigilance function are outlined in table I.

There may be disagreement about what constitutes 'promotion' versus 'balanced risk communication'. Indeed some marketing professionals may re-

Table I. Myths about those who work in pharmacovigilance

Idealistic perfectionist – never satisfied
Head of sales prevention
Bringer of bad news
Not committed to product success
Always wanting more resources and not interested in business efficiency
Rigid and unwilling to be creative: 'rules are rules'

gard it pejorative if their role is described primarily as concerned with 'promotion'. Clarification about terminology is crucial to ensure mutual understanding particularly by avoiding terms with imprecise meaning such as 'side effect' and 'adverse effect'. The concept of 'safety' should be better explained in terms of balancing risks and benefits. Certain terms may unduly alarm because they mean something different to different people. In this respect, paradoxically the terms 'pharmacovigilance' and 'risk management' are often best avoided. It is best to discuss tasks and activities of common interest where cooperation may be possible. Instead of the words 'risk' and 'management' I suggest the words 'issue', 'strategy' and 'activity', which are less emotionally charged. Marketing may be comfortable talking about 'knowledge management', which could be used synonymously instead of risk management. The conversation should be de-personalised and non-judgmental maintaining a focus on the common goal or desired outcomes for all. We can empathise how difficult it can be at times to communicate difficult messages without being false and misleading. This is particularly so when an adverse reaction might offend customers even though medically it may not be serious. By developing a dialogue you may be surprised to find that there is more common ground between 'pharmacovigilance' and 'marketing' than you might at first believe.

We should be sensitive to the concerns of marketing about 'sales prevention' and 'drop in revenue'. These concerns should be aired and marketing asked to be more specific about what underlies their fears. They can be reassured because, as described in many companies' annual reports, all who work within a company should be motivated to support the product and work to recoup the significant financial investment required for developing a new chemical entity in 2004.

A concern among those within pharmacovigilance might be that too close a collaboration with marketing may lead to a dilution or blurring of values. Thus when integrating PRM with marketing activities I suggest some ground rules are required to help ensure compliance with the principles of pharmacovigilance. For practical purposes, I suggest these can be extrapolated from the European Union (EU) guidelines for post-authorisation safety studies as follows:[2]

- activities should be consistent with normal prescribing practice, to take account of all patients likely to receive a product and be as close as possible to real-life;
- there should be a balanced comparison with normal therapy(ies);
- activities should not be perceived simply as a promotional and one-sided exercise but should be based on scientific need and logic;
- remuneration of health professionals should reflect time and expenses incurred which in itself often requires scientific judgement;
- metrics should be agreed about how to measure the impact of activity, including the decision of 'no action required';
- an adequate level of documentation is required to record what happened including regular activity or study reports.

One area to consider is whether to disentangle marketing from sales, in the sense that those who actually negotiate financial contracts with healthcare systems should be kept separate from the rest of the company. This would help lead to development of a more scientifically robust postmarketing department, which makes full use of its expertise.

4. Why Would Those Who Work in Marketing Want to Collaborate with Those in Pharmacovigilance?

Apart from the ongoing regulatory discussions about risk management and pharmacovigilance,[3] there are other ethical, social, financial, legal and regulatory pressures pushing pharmaceutical companies to become more transparent in the way they behave, comply with regulatory expectations and represent the benefits and risks to their customers. I would suggest that these are the types of argument that can be politely brought to the attention of those working within marketing.

4.1 Ethical Reasons

To retain public confidence in healthcare systems, which include the pharmaceutical industry, there is pressure to demonstrate corporate integrity and develop a compliance culture.[4] All physicians,

including those who primarily have a role in the pharmaceutical industry, are subject to ethical responsibilities and these have been recently reaffirmed: "The central moral objective of medicine – adhered to by doctors and healthcare workers since Hippocratic times – is to produce net medical benefit with as little harm as possible. Today we may add to that Hippocratic objective the moral qualifications that we should pursue it in a way that respects people's deliberated choices for themselves and that is just or fair to others (whether in the context of distribution of scarce resources, respect for people's rights or respect for morally acceptable laws)".[5] Such views are reflected in the Declaration of Helsinki, where the importance of balancing risks or hazards and benefit is mentioned or, at least inferred, five times. According to the Council for International Organizations of Medical Sciences (CIOMS), 'research' is any activity designed to develop or contribute to generalisable knowledge.[6] Finally, certain therapeutic areas (such as contraception, gene therapy, fertility) are morally complex with an array of different national legislation, interested groups and cultural differences to consider. These complex ethical therapeutic topics are good examples of why there is a greater need for pharmacovigilance and marketing to work together to identify and meet the needs of all customers, be they patients, prescribers or governments. I would argue that as the emphasis on pharmacovigilance is on balancing benefits and risks in the interests of patients, it should claim its rightful place at the heart of corporate integrity for the pharmaceutical industry.

4.2 Financial Reasons

Within the industry, there is greater realisation that the traditional one-off endorsement for a product, once a marketing authorisation is granted, has now really been replaced by the need for continuous evaluation of risks and benefits. Discussing the need for PRM planning should no longer be a surprise particularly as safety is a priority area in many different industries. Managing the risks of marketed products is the price of doing business for other industries as well. The automobile industry is an example of another industry manufacturing a high-demand consumer product that had to develop a culture of consumer protection, which has now become a key element in its marketing strategy. Before 1975, the common view of automobile executives was that they could control any part of the automobile right down to the last nut. In the last decades, however, many innovations, which have made cars attractive, have been designed to protect drivers from their own mistakes, including seat belts, airbags and anti-lock braking systems. More explicitly, some high-risk industries have voluntarily adopted the concept of product stewardship. This concept is defined by Chevron Texaco as the management of the environmental, health and safety impacts of its products throughout their entire life cycle.[7] The Chemical Industries Association provides a simple outline for a company to start product stewardship, identify what has to be done and prioritise its efforts. The management cycle described to achieve these objectives looks remarkably similar to the risk management framework described by the US FDA.[8]

There are evolving changes in marketing practice, which will act in favour of adopting PRM. The nature of new chemical entities has changed with many new innovative medicines targeted on secondary care rather than primary care. This would mean a smaller sales force who are more scientifically trained to converse with specialists. The FDA has hinted that there may be a role for the sales force in PRM although no details were provided about what would be deemed acceptable.[9] However, the FDA suggested that they expect sales representatives to have appropriate incentives for providing balanced-risk information.[10]

New medicines now tend to be promoted on the basis of the specific disease state rather than whether or not they work better than their competitor products. There has been a shift in power away from industry towards the 'purchasers' such as governments or healthcare providers. Evidence for this include the establishment of organisations such as the UK based National Institute for Clinical Excellence and the reforms occurring in the US Medicare system. These purchasers more commonly seek objective evidence of medical results. A substantial part of the value that companies offer will be services that accompany the product. These services can often form the backbone of a comprehensive support network that helps individual patients to

identify when they really need to see a doctor, to help them manage the disease state with non-pharmacological measures and understand better why they should continue taking their medicines and the need for monitoring. Such a support network can form the basis of a voluntary 'risk-management plan'.

This marketing pressure on products is aggravated by lack of productivity in the laboratory, patent expiries, intense therapeutic competition and above all, a steady rise in the cost of developing products. Part of the suggested business solutions is to develop a customer-driven approach and develop an integrated business model.[11] Indeed the FDA anticipates use of the marketing budget for PRM.[12]

4.3 Social, Legal and Regulatory Pressures

Over the last few years, the US industry in particular has been hit by a few major corporate scandals which has severely dented investor confidence. As part of the effort to restore investor confidence, the Sarbanes-Oxley law on corporate reform was passed in the US to improve financial accountability and transparency. But, as described by the Chairman of US Securities and Exchange Commission to improve corporate governance "what's really needed is not necessarily more laws but rather the full engagement of business leaders in an effort to advance an underlying spirit of reform. These reforms must inculcate a company wide mindset to do the right thing and must become part of the DNA of the corporation from top to bottom."[13] These concepts are similarly reflected in compliance programme guidance published by the US Office of the Inspector General.[9] Some lawyers have stated that inadequate reporting of adverse reactions (such as during a switch programme) might fall under the broader meaning of the US federal anti-kickback statute.[4,14,15] The criminal sanctions that might result from a successful prosecution could be considerably punitive. In this respect, the successful prosecution of the company Endovascular Technologies for ten felonies, with charges of $US92.4 million (for covering up thousands of adverse incidents where their device malfunctioned), is a landmark case.[16] With 40% of a typical product's global sales and 60% of profits occurring in the US market,[17] changes here in marketing practice are likely to have a global impact.

As I discussed earlier, I believe pharmacovigilance should be considered part of 'doing the right thing' and the foundation of compliance culture. It is logical to argue that inadequate benefit-risk assessment within a company might lead to misrepresentation of the commercial value of the product thus linking pharmacovigilance to financial corporate governance. I suggest that both investors and governments would be reassured that balancing benefit and risks for patients was engrained within a company's culture.

PRMs offer opportunities to marketing groups to more effectively tackle difficult areas under increased regulatory and legal scrutiny such as off-label use. Provided there is at least some evidence of efficacy, then within a PRM and after having received regulatory permission, a company might be able to legitimately provide prescribers with risk information, which might pertain to a particular unauthorised indication. Finally, the image and reputation of a company can be damaged if prescribers are concerned by the conduct of marketing studies, excessive remuneration from industry and inadequacy of arrangements for reporting of suspected adverse reactions.

5. Changes That Have Already Occurred in Company Attitudes to Product Marketing

By means of public statements of intent, the pharmaceutical industry has committed itself to the core values of pharmacovigilance. For the EU, the European Federation of Pharmaceutical Industries and Associations has stated that: "all medicines in the enlarged EU meet the highest standards of quality, safety and efficacy".[18] For the US, the Pharmaceutical Research and Manufacturers of America makes a similar commitment: "pharmaceutical companies and the FDA take as a primary responsibility the duty to ensure safe use of all approved medicines in the US….the principal concern of both the agency and the industry is that patients receive medicines that have been demonstrated in every reasonable medical, scientific and practicable way to provide more benefits than risks when used appropriately in accordance with label instructions". Thus, if we look

forward, rather than dwell on past errors, any attempt by industry to take a more pharmacovigilance-orientated approach to marketing should be welcomed even if the company itself does not call it 'risk management'. There is some evidence that suggests that within the US some companies, intentionally or not, are voluntarily adopting principles consistent with some aspects of risk management as part of their marketing strategy. This is best illustrated for medicines which are associated with medical errors or which have a high public profile. Examples include Bristol Myers Squibb who have provided support to help patients manage their own warfarin therapy to help achieve more effective outpatient anticoagulation and prevent complications and Barr Laboratories who, after having conducted studies to test whether women understood labelling for their over-the-counter contraceptive Preven (Plan B)®, have promised to plan a campaign to support users including a patient educational campaign and 24-hour hotline.[19,20] Without inside knowledge we cannot judge the epidemiological rigour of such programmes but we can acknowledge these as welcome efforts to reduce product risks and learn by observation how effective they are. A different approach has been taken by GlaxoSmithKline in Florida where they announced that they would design a programme that will include: "understanding the causes and consequences of medication errors in Medicaid beneficiaries and developing systems to reduce errors in medication administration". This is thought to be one of the first of its kind. Pfizer and Bristol Myers Squibb had already started disease-management programmes in Florida although these initiatives are more tied into pharmacoeconomics and cannot be directly linked to PRM.[21] Admittedly as these programmes are entangled with attempts at trying to reduce the costs of the state Medicaid programmes, they can lead to different priorities and outcome measures of success for the stakeholders, which is a wider scope of objectives than only pharmacovigilance. However, any attempts to develop a collaborative approach, which will benefit patients, should be welcomed.

Changes in future EU legislation adopted by the European Parliament for the EU, community code (Dir 2001/83), and due to be published this year will state that marketing authorisation holders should ensure that information is presented objectively and is not misleading. The German Pharmaceutical Industry Association has responded with recommendations about how pharmacovigilance responsibilities and decision making about benefit and risks should be structured within companies. This includes appointing an expert committee with multiple functions including routine consultation with marketing personnel, if health damage was suspected or had occurred or if special measures were required.[22]

6. What Marketing Has to Offer to Pharmacovigilance

When looking at risk-management plans, which are based on FDA requests, it is obvious how controlled marketing of the product is regarded as critical to a successful PRM.[23] I am interested in exploring how companies can more effectively utilise voluntary PRM. Apart from controlling distribution, which is rather drastic and invasive for most products, I suggest we should turn our attention to one of the main attributes of marketing, which is to communicate the evidence supporting the benefits and risks of a product in a way, which is neither false nor misleading. This activity is performed in a free-flowing and imaginative way invariably without standard operating procedures (SOPs) and customised for each product. Throughout drug development, the role of marketing is to understand when recipients are ready to receive particular messages and what sort of priority the message will be given. The decision to commence marketing activities often coincides with the decision for the product to undergo first testing in humans. Of course, this would be the ideal time for starting a PRM.

As part of the rolling marketing plan throughout drug development, a company will identify, characterise and prioritise issues and then develop different strategies focused on addressing key issues. It is noteworthy that the words 'issues' and 'strategies' appear in the FDA's description of a risk-management framework. Thus with successful collaboration a company's issues could be bundled together and from these strategies and subsequent actions can arise. For instance, marketing departments may ask epidemiologists to design studies to better define the target disease for a product, the results of which may

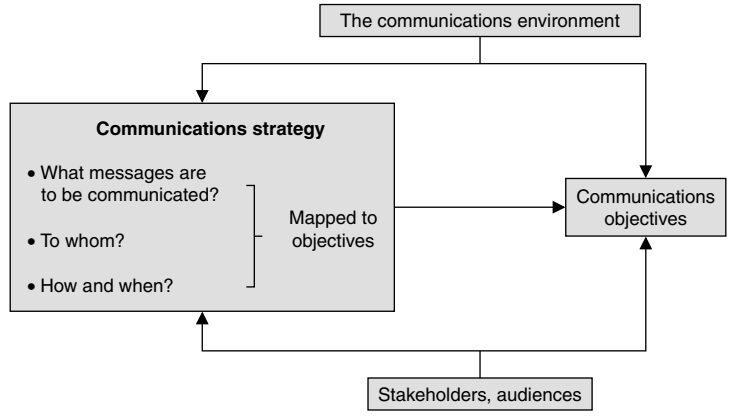

Fig. 1. Communications strategy.

interest many within a company. Although marketing activities may not operate to SOPs, this does not imply unclear and random behaviour patterns are the norm. Objectives of a plan should be specific, measurable, achievable, realistic and time bound and there are usually written plans ('protocols') about how they will be achieved. It is such an unimpeded imaginative approach, combined with adequate documentation and measurement of impact, which is required in designing a PRM (whether it be voluntary or for regulatory submission). The details of regulatory compliance can be added once the plan has been designed.

6.1 Marketing Can Help Design Communication Strategy

Although conventional forms of communication, such as 'Dear Doctor Letters' can have an important impact, they cannot be relied upon on their own to change behaviour. Based solely on a scientific analysis of the evidence, there are no guaranteed ways of always communicating risks and changing health professional behaviour and ideally further research is required to establish the most effective strategies.[1,24]

A marketing group will have identified all relevant stakeholders, that is, all those with a vested interest in the product. Stakeholders are part of the wider audience, which nonspecifically watches everything a company does and says. Both groups need to be accommodated within a successful communication strategy. With a marketing department's knowledge of both groups, communications can be customised (figure 1). The principle behind this is to determine how a target audience currently perceives the risks and benefits of a product compared to the way a company would like the product to be perceived. This shift in perception is determined by the way a company assembles and presents the evidence about benefits and risks, which may include performing more work to better understand prescriber or patient behaviour.

In addition to written communications, a typical communications programme may consist of all or some of the following, which are usually arranged within a company's marketing department.

- Expert advisory panels: Marketing people, often working with others on a product development team, are experienced in arranging such panels from selecting the venues and on-site logistics through to executing the meeting. These panels may be convened to discuss benefits and risks of a product.
- Investigator relations: It is the role of marketing to legitimately convert pre-authorisation investigators into post-authorisation advocates for the products. They have a responsibility to maintain contacts with interested physicians at a local and global level by providing help for speaker training, lecturing materials, sponsoring meetings and maintaining a support centre often through a web site. Continuing medical education is an important part of implementing an advocacy network.[12]

- Focus groups: According to the FDA risk-management framework, focus groups should be convened to consult external stakeholders in the development of a product. Often companies use a field agency to provide a moderator for the focus group and the expertise to write up and analyse the results. In several locations, a focus group should be composed of relevant professionals – physicians from the relevant therapeutic area and possibly also nurses or other health professionals or the group can consist of appropriate patients.
- Publication planning and delivery: Currently, within a company, marketing decides how best to ensure how and when data are to be written up, who the target audience should be and what the key messages should be.

It is plausible that should a company wish to improve the efficiency of its operations that the activities described above can be integrated to meet not only the needs of risk communication but also the wider needs of the company. If this is for regulatory purposes, this may involve more documentation to demonstrate how decisions were reached and that appropriate actions were taken (so that an inspector might know and understand what happened). However, as the scale of such documentation is at the discretion of a company and for some countries already has to meet existing marketing regulations,[4] this may merely mean modifying what was being executed. As part of assessing the impact of a communications programme and materials, further focus groups or surveys to elicit prescribers' and consumers' opinions can be performed. Other forms of pharmacoepidemiological studies may be considered as well.

6.2 Marketing Support for Investigator Recruitment and Retention

One important area where marketing techniques are increasingly being implemented is investigator recruitment and retention particularly for large pre-authorisation clinical trials. Although companies use similar techniques readily for voluntary post-authorisation studies, there is no regulatory reason why the same techniques cannot be applied with the same enthusiasm to post-authorisation commitment activities including post-authorisation safety studies. The reason is simple: all post-authorisation studies should be performed to the same regulatory standards regardless of whether they are a regulatory requirement or not.

7. Conclusions

The purpose of this paper is to raise awareness of the activities that companies already perform which could be adapted to PRM. In some companies, scientific activities are already performed by marketing, which could be recognised as PRM even though they might not be called that. Thus misconceptions about roles and responsibilities within an organisation and semantics, in the sense that certain terms mean different things to different people, threaten to slow down a company's progress in developing best practice in pharmacovigilance and risk management. I would argue that as all within a company who are involved in product development are bound by the principles of the Declaration of Helsinki, they automatically have a pharmacovigilance responsibility. However, we should not expect rapid change but more of a gradual evolution within marketing towards a greater appreciation of the value of an evidence-based approach to balancing benefits and risks with the patient (customer) at the centre. With financial pressures on product development and global pressures to reduce risks, I would argue from a business perspective alone, that companies should look very closely at their own internal relationships to see how best to implement the principles of PRM. In pharmacovigilance we are used to taking action even when evidence is incomplete or under imperfect circumstances. The bottom line is, wherever you work within a company you should all have the common business desire of identifying and meeting the needs of your customers. Corporate integrity should be fostered based on pharmacovigilance and become part of the company branding. In the case of PRM, this is about effective working together to achieve an acceptable balance of risks and benefits.

Acknowledgements

This article has been based on considerable input from Dr Paul Williams, Tom Snyder and their colleagues from Medical Marketing Services, PAREXEL International.

The views expressed in this paper are solely those of the author and do not necessarily reflect those of the wider PAREXEL corporation.

Dr Edwards is an employee of PAREXEL International which is a global contract research organisation which provides a wide range of product development services to the biopharmaceutical industry.

References

1. Perfetto EM, Ellison R, Ackermann S, et al. Evidence-based risk management: how can we succeed? Deliberations from a risk management council. Drug Inf J 2003; 37: 127-34
2. ICHE2E Pharmacovigilance planning: Note for guidance of planning pharmacovigilance activities (CPMP/ICH/5716/03)
3. Company-sponsored post-authorisation safety studies. Vol. 9 [online]. Available from URL: http://www.pharmacos.eudra.org/F2/eudralex/vol-9/pdf/Vol9en.pdf [Accessed 2004 May 12]
4. Benefits of a compliance program. Office of Inspector General Compliance Program Guidance for Pharmaceutical Manufacturers. April 2003
5. Bridging the gap between theory and practice: the BMA's approach to medical ethics. Medical Ethics Today. 2nd ed. Oxford; BMJ Books 2003: 1
6. Council for International Organizations of Medical Sciences (CIOMS) International Guidelines for Biomedical Research involving Human Subjects 2002
7. ChevronTexaco 2002CR Report: Product stewardship [online] Available from URL: http://www.chevrontexaco.com [Accessed 2004 May 6]
8. Managing Product Stewardship [online]. Available from URL: http://www.cia.org.uk [Accessed 2004 May 6]
9. US Food and Drug Association (FDA) sees risk management role for sales forces; Drug Safety Cmte. Coming. The Pink Sheet, November 12, 2001: 16-7
10. Rx Sales Incentives Should Encourage Risk Education, AMA Tells FDA. The Pink Sheet, May 27, 2002: 6-7
11. Gilbert J, Henske P, Singh A. Rebuilding Big Pharma's business model. In Vivo 2003 Nov; 21 (10): 1-9
12. Pharmaceutical Research and manufacturers of America (PhRMA) marketing code is shifting promotional budgets to CME The Pink Sheet November 4 2002: 11
13. Donaldson W. Not by rules alone. The Economist The World in 2004, 134
14. Bass S, Sarraille W. Emerging government fraud and abuse theories require new brand of risks assessment Rx Compliance report 2003 Nov 11; 11: 1-4
15. ADR cases could be prosecuted under kickback statute- U. S. Atty Sheehan The Pink Sheet 2002; Sept 16: 11
16. Justice Department. Civil fraud recoeries total $2.1 billion 2003 [online] Available from URL: http://www.usdoj.gov/opa/pr/2003/November/03_civ_613.htm
17. Europe's position in a global market [online]. Available from URL: http://www.efpia.org/2_indust/europe_0.htm [Accessed 2004 May 6]
18. European Union enlargement and pharmaceuticals: key issues [online] Available from URL: http://www.efpia.org/2_indust/topic_2.pdf [Accessed 2004 May 6]
19. Bristol-Myers Squibb Company. Coumadin (warfarin sodium tablets) [online]. Available from URL: http://www.coumadin.com [Accessed 2004 May 6]
20. Preven online Care Centre [online]. Available from URL: http://www.preven.com [Accessed 2004 May 6]
21. Florida Medicaid in the spotlight: GSK Error Program is latest experiment The Pink Sheet 2003; Feb 3: 8-9
22. ISOP Presentation Communicating about Risks Prof Dr Barbra Sickmuller Bundesverband der Pharmazeutischen Industrie (BPI) Berlin, Jan 30th 2004
23. Lilly Forteo Risk Management Program Limits Launch to 8,000 Doctors The Pink Sheet Dec 16, 2002; 7
24. Campbell WH, Califf RM. Improving Communication of drug risks to prevent patient injury: proceedings of a workshop. Pharmacoepidemiol Drug Saf 2003; 12: 183-94

Correspondence and offprints: Dr *Brian Edwards*, Pharmacovigilance Specialist, PAREXEL International, The Quays, 101-105 Oxford Road, Uxbridge, UB8 1LZ, UK.
E-mail: brian.edwards@parexel.com