EDITORIAL

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Risk Management of Medicines and Compensation for Harm

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1. Current Compensation Practice

Total drug safety is impossible to attain, and there are many cases of drug injury that go to court where negligence may not be the issue, although the injuries are dire. Here are two examples: a woman with epilepsy whose two offspring have fetal valproate syndrome;[1] and gangrene and amputation following phenergan injection.[2] In both situations there were extant labelled warnings. Such cases may be considered within the concept of strict product liability under which, essentially, the cost of any harm caused by a product is borne by the producer.[3,4]

Huge costs are incurred by safety problems with medicines, which affect all stakeholders: patients, healthcare providers, insurance companies, public health services and the legal system. Because of the high cost there is reluctance to pursue litigation in some cases, particularly when one obvious consideration is that some patients may experience considerable harm from a drug despite warnings and its appropriate use. Even if the case is funded, the expense of running it and the risk of having to pay costs of both sides if the case is lost are seriously prohibiting factors: funding and cost problems are major deterrents to litigating cases involving drug therapies.

Litigation runs counter to the aspirations of the new patient safety considerations: to create no blame reporting of harmful, and potentially harmful, situations. The aim is to promote a milieu of trust, understanding and action in which wrongdoing is not punished but all the surrounding causative factors are found and minimized or eliminated. The approach is based on the principle that it is systems that are to blame and not people.[5-7] Although systematic errors may be common reasons for human error, wilful actions do occur when competing motivations lead to unethical action likely to result in legal accountability.

All-in-all, the current situation provides little incentive for safe medicines and therapy, only punishment for failures. The regulatory system, being heavily concerned with process compliance, is heavily bureaucratic, because it tries to spot and manage small infringements with the aim of thus preventing major problems. The bureaucracy is also fuelled by distrust, mainly related to the motives of the lucrative pharmaceutical industry,[8] and there is media and public concern over the whole drug safety area.

2. The Limitations of Safety Monitoring and Prevention

Current drug safety monitoring is limited for the following well known reasons:

- The efficacy of a product in controlled clinical trial situations may differ from effectiveness in real life practice when more extremes of disease severity may be treated.
- Relative effectiveness and risk of a new product against older treatments is mostly not known.
- Both effectiveness and risks might be affected by concurrent disease and coadministration of other drugs; situations that have been avoided in clinical trials.

- Much medication error, which may be systematic (relating to dosage form, packaging, information, clinical use and misuse – including off-label use) is avoidable.
- Current information on the effectiveness and risks of medicines has little impact on practice.
- There is very little audit of the impact of pharmacovigilance knowledge on improving public health.

These considerable gaps in our knowledge of products on the market are considered to be part of the market authorization holder's (MAH) responsibility as 'good stewardship'. Considerable MAH effort is put into seeing that case harm reports and summary information to regulators are quality assured and timely.

Academia and healthcare providers also determine the relative effectiveness, and risks, of treatments, including specific drug products, usually without either regular funding or complete access to evidence.

Consequences of the current situation are as follows:

- The industry is placed in the dilemma of being the major player in collecting and analysing the risk information on their products, knowing that public knowledge of risk might affect their products' profitability.[8]
- Similarly, evaluations of relative effectiveness might also result in conflicts relating to sales and profitability for industry.[8]
- Industry carries the financial costs of loss of market share and poor reputation, as well as the costs of litigation when negative information on its products is brought to light.
- About half the burden of harm from drugs is known and possibly avoidable. The responsibility for evaluating and remedying this avoidable risk is unclear.
- Insurers, lawyers, clinical health professionals and the media have a very significant role to play, which is different from the public health gaze of regulators and industry: they focus primarily on the minority who suffer damage from drugs and the way they are used.
- Patients face the daunting and terrible prospect that, for whatever reason, the drugs they use may cause morbidity and death.

The dichotomy of view between those whose role it is to consider overall public health effectiveness and risks of drugs by epidemiology and those who deal with the actual benefits and harm to individuals are often in some conflict, but none would disagree on the principle of preventing harm to minorities, nor on the compensation of individuals when negligence by a party leads to harm.

3. No-Fault Compensation

A no-fault compensation scheme for the minority of people who experience serious and protracted harm or death from drug products seems ethically correct and, based on strict liability logic, the producer should be the funder.

To place the onus for all compensation on MAHs does ignore the knowledge that perhaps half of the hospital admissions for adverse drug reactions are 'avoidable', or certainly known, based on current product information and published information. These situations suggest considerable responsibility should rest with the prescriber, dispenser and user of the drug product and their employers/insurers.

4. Risk Management

Both the EU and the US are promulgating risk planning as part of the registration of drug products. The idea is that pre-clinical information on animal toxicology, harm seen in human experimental subjects, knowledge of drug products with similar chemical structure or pharmacology, the possibility that the drug may be widely used in vulnerable groups of patients (e.g. children) and other factors should lead to post-marketing surveillance that will illuminate those risks as soon as possible.

MAHs should provide plans on how to manage any significant risk they identify with their products, which should include effectiveness/risk evaluation and re-evaluation in the post-marketing clinical situation, strategies to mitigate risk and enhance effectiveness, and communication of useful information for healthcare professionals and patients. Current drug regulation

focuses on proof of safety and efficacy, and often a license fee is paid by the MAH for regulators to evaluate the data they provide prior to marketing. There is also a fee paid by MAHs for the regulators to evaluate data periodically to support the maintenance of a product on the market. Currently, regulators take a large role in the assessment of a medicinal product for marketing but a much less active role in the post-marketing period.

5. Proposed Development to Incorporate Risk Management and No-Fault Compensation

For progress to occur, there needs to be incentives for the delivery of safe medicines by all those concerned with their provision. As part of this, it seems advantageous to have a no-fault system of compensation for those unfortunate enough to experience serious adverse effects from therapy, because not all harm will be avoidable.

First there must be a complete analysis of the costs of harm from medication and how it is currently spread amongst stakeholders. Saving MAH money on disruptive crises, costly litigation, insurance, loss of market share and reputation must be major incentives. Saving costs for healthcare providers and insurers must be another major driver. Safety could be seen as a marketable commodity: to see lack of harm as a benefit, both to individuals and society.

The new risk management planning approach could be turned into a very positive benefit for pharmaceutical industry. Starting at registration of a new product, instead of a flat fee, the levy could be reduced for products likely to have more public health benefit and for products with good risk management proposals. Justification for the reduction should form part of the registration, and would have the benefit of encouraging those products with clear advantages, as compared with 'me-too' products. If cost-benefit were also included, generics would also be encouraged. It will be argued that such a scheme will be dependent on value judgements by the regulatory authorities; similar judgements are currently made for inclusion into reimbursement lists in several countries.

Re-registration fees would be considered similarly, and it should be possible to measure performance by the company against its risk management goals decided at registration, as well as proposals for new risk management strategies.

The registration fees charged should cover serious drug-induced disease, including the unavoidable component, and a substantial part of the avoidable cost. This may seem unfair, but the aim is to encourage MAHs to pursue active strategies of risk management, bearing in mind the benefits that will accrue through reduced fees for their success.

Some of the provision for compensation should be through healthcare providers since they should play their part in improved use of medicines and safety. Their contribution might be moderated via an audit process akin to the certification schemes used for healthcare facilities in the US. In these schemes, audit of procedures, such as the ability to identify and remedy systematic causes of medication error, play a role in maintaining certification of a facility.

The compensation provided to individuals who have experienced adverse effects from drug therapy should only be for substantial and long-term injury or death. A separate authority will be needed to judge causality. It should not be possible for a claimant to directly take legal action against an MAH for injuries. It should, however, be possible for regulatory agencies to act against the MAHs for withholding information and to impose penalties for negligent performance. It is not envisaged that this will be common.

6. Advantages

Many advantages should accrue from the approach discussed here.

- The potential benefits and risks of products will be evaluated in a much more scientific and open way than at present.
- Drugs with more benefits and less risk will be encouraged.
- The cost of drug-induced disease should be reduced, both in levels of suffering and in financial impact.

- The reduction in financial impact will benefit industry by a general reduction in license fee, as well as through good risk management.
- MAHs will be free of claimant litigation. That they actively contribute to a no-fault scheme will generally enhance industry claims that they work for the good of public health.
- The activity of drug regulation will extend beyond the point of registration to an active concern over whether the best and safest use is made of a product in real clinical situations.

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