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From Pharmacovigilance to Pharmacoperformance

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Abstract

The pharmaceutical industry is going through a period of enormous upheaval, as new sciences, technologies and commercial pressures reshape the way in which it performs research and development. PwC Consulting estimates that the top 20 companies will each need to launch between four and six times the number of drugs they currently produce, as well as improving the quality of those drugs, merely to maintain shareholder returns. This has huge implications for pharmacovigilance departments. More drugs means more trials, more patients and – of course – more safety reports for evaluation. The pharmacovigilance teams in most big companies are ill prepared for this transition being already stretched to the limit. But as demand for patients to participate in clinical trials increases – with shorter development times, higher success rates in discovery and greater productivity – so companies with a poor reputation for safety will suffer.

What is it then that companies should be doing to remain compliant and be seen to be safe in the eyes of the consumer? Can pharmacoepidemiology support both molecules in the marketplace as well as those in research and development and what is really needed to enable this?

Key to success will be the ability to capture, analyse and evaluate data (from disparate sources) in real time and to make rapid decisions on the appropriate course of action. Putting better structures, processes and technological platforms in place to cope with a big increase in throughput is only a short-term solution yet is it enough to fulfil the objective in the long-term of ensuring compliance and patient safety?

The pharmaceutical industry is going through a period of enormous upheaval, as new sciences, technologies and commercial pressures reshape the way in which it performs research and development. In one of several reports on the sector, *Pharma 2005: An Industrial Revolution in R&D*,[1] PwC Consulting estimates that the top 20 companies will each need to launch between four and six times the number of drugs they currently produce. They will also need to improve the quality of those drugs, if research and development costs rise in line with past performance and if shareholder returns are to stay the same. This has huge implications for pharmacovigilance. More drugs means more trials, more patients and – of course – more safety reports.

But the increase in its workload (figure 1) is only part of the story. Massive changes in the industry's working practices will arguably have an even greater impact, since they will change its very

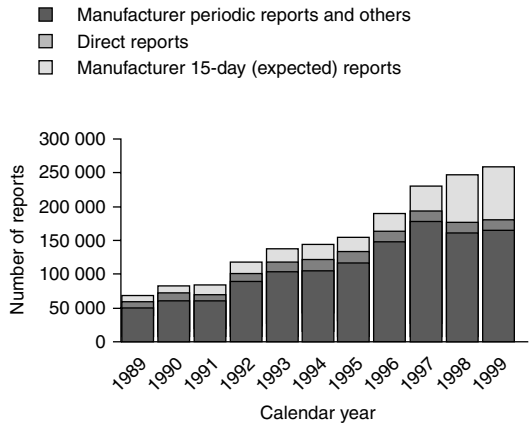

Fig. 1. Number of postmarketing adverse event reports received by the US Center for Drug Evaluation and Research by year.

role. PwC Consulting's second report in the *Pharma 2005* series, *Silicon Rally: The Race to e-R&D*,[2] shows how emerging technologies will transform the way in which drug discovery and development are conducted. The advent of e-research and development will, in turn, change what pharmacovigilance does. It will move from reactively monitoring drug safety to proactively ensuring drug performance.

The pharmacovigilance teams in most big companies are ill prepared for this transition. They are already stretched to the limit. Many are also as undervalued as they are overworked. In an industry that prizes intellectual curiosity, the collation and evaluation of data on the safety of drugs, devices, diagnostic testing kits, nutraceuticals and the like is all too often seen as a poor relation to research.

But as demand for patients to participate in clinical trials increases (with greater productivity in discovery, higher success rates in development and shorter time scales throughout the whole innovation process), and as advances in pharmacogenomics render adverse events less acceptable, companies without a strong reputation for safety will suffer. What is more, it may take very little to tarnish a corporate good name. Consumers are becoming better educated and more knowledgeable. The power and reach of the Internet will also soon be such that stories about the adverse effects of a drug may have an impact out of all proportion to the events that triggered them.

In the short-term, then, the question is whether the industry's pharmacovigilance functions can put better structures, processes and technological platforms in place to cope with these significantly higher expectations for performance. In the longer term, this is like topping up the oil in a car that needs a new engine. The challenges facing pharmacovigilance will require far more radical treatment.

1. Getting it Right the First Time

Most pharmaceutical companies outsource a growing amount of development work; the percentage of projects involving clinical research organisations is now 60%, up from 30% just 6 years ago. They are also increasingly reliant on information from other external sources – such as investigators, health management organisations and patient groups conducting self-administered trials.

The impact on the pharmacovigilance team is obvious. It has to deal with many more, and more disparate, sources of data on drug safety. Yet, typically, it is people in clinical development – not pharmacovigilance – who design the protocols for collecting information on adverse events. This means that vital details are often omitted first time around. But the greater the delay in collecting such information, the harder it is to resolve any differences of opinion about a particular adverse effect. Moreover, the regulatory clock has already started ticking and, if anything goes wrong, it is not just the regulators that will be up in arms. The media and consumers will also want a rapid and accurate response.

Two changes would overcome many of these difficulties. If the pharmacovigilance team were involved in drafting the forms for safety reporting, it could ensure that those forms were designed to elicit all the evidence it needed, regardless of therapeutic category. With the introduction of electronic adverse event reporting systems to automate

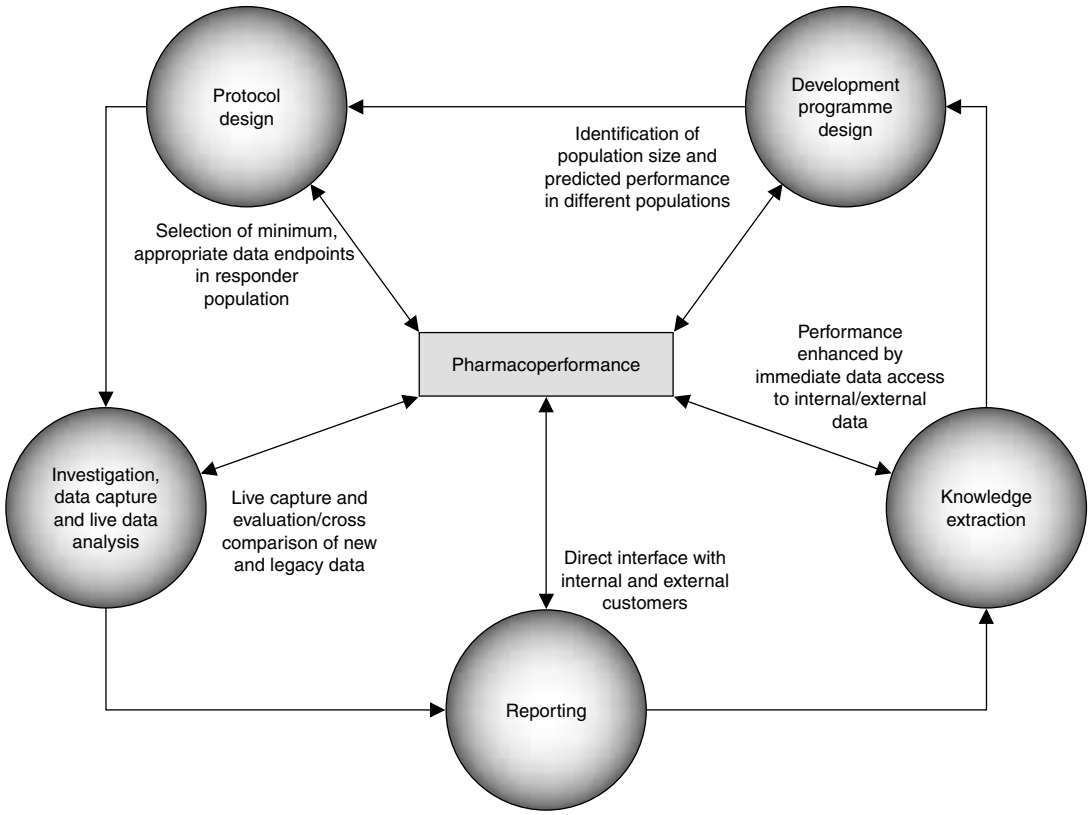

Fig. 2. Future key contributions of pharmacoperformance to successful product development.

the collection of case reports, wherever they originate, it could also access those reports much more promptly. In short, if it is to get the data it needs when that data is needed, pharmacovigilance must become an integral part of the research and development network (figure 2).

2. Designing for Safety

There are other good reasons for taking this route. Research by Dr Carl Peck, Director of the Center for Drug Development Science at Georgetown University, Washington, USA, shows that front-loading trials with data derived from other, similar drugs would significantly improve the clinical development process and accelerate drug selection.[3] It might eventually also lead to more judicious and more limited data collection. Although the US Food and Drug Administration (FDA) currently requires only two pivotal efficacy trials for approval of a new drug application, the average number of trials supporting each submission is now 68 – up from 30 in 1984. Furthermore, the FDA reports that 25 to 50% of those trials fail to meet their objective.[4]

As the repository of knowledge on drug safety profiles and epidemiology, the pharmacovigilance operation thus has a pivotal part to play in predicting the toxic effects of related compounds and designing suitable trials. Far from being a service provider at the end of the research and develop-

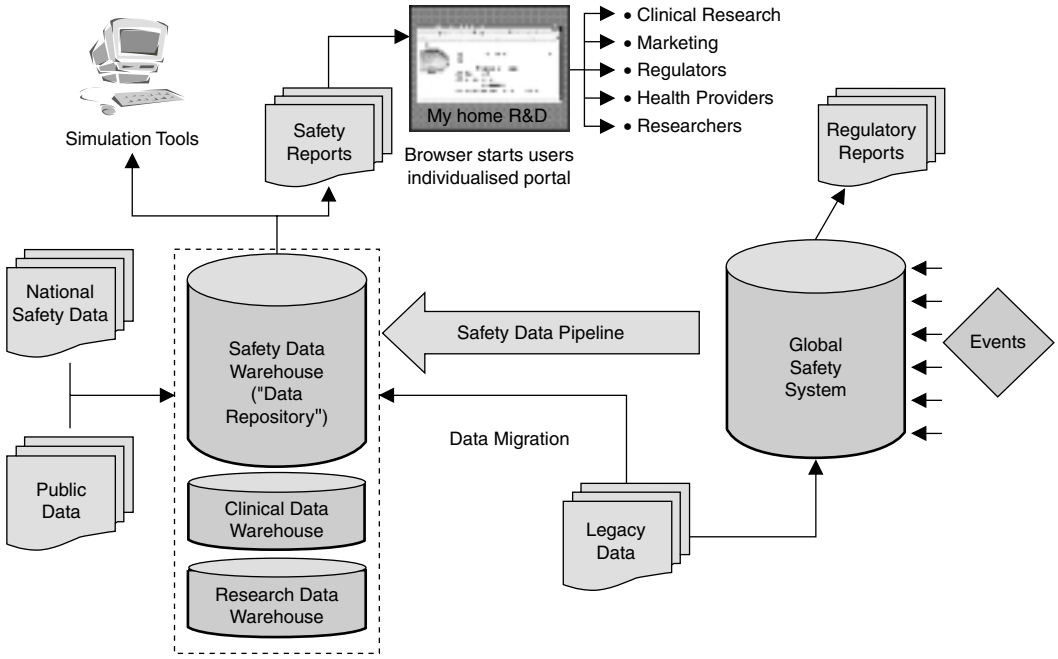

Fig. 3. Conceptual overview of pharmacoperformance.

ment chain, it should be intimately involved in the clinical development process.

3. Assuming a Greater Burden of Proof

The proofs of safety that pharmacovigilance is expected to deliver are also likely to grow, as scientific and technological advances raise the expectations of regulators, healthcare providers and patients alike. In its *1998 Report to the Nation*, the FDA's Center for Drug Evaluation and Research (CDER) stated that 'injuries from approved medicines rank among the top ten causes of death in the US'.[5] The economic cost of such injuries is also considerable. One study, published in *JAMA* in 1997, puts the cost of adverse drug reactions in a 700-bed teaching hospital at $US5.6 million a year.[6]

Clearly, some adverse reactions stem from improper use rather than innate toxicity or individual sensitivity. But with the application of pharmacogenomics and *in silico* technologies, the industry should soon – theoretically at least – be able to predict precisely which groups of people will respond well or badly to a particular medication, both in clinical trials and in the marketplace (figure 3). Thus both the regulators and healthcare providers are likely to become far less tolerant of 'avoidable' adverse effects and far less sympathetic to the need for post-launch withdrawals or modifications of a drug or its labelling – a trend that will place a much heavier burden on the pharmacovigilance operation.

In fact, the position pharmacovigilance occupies – midway between clinical development and marketing – may also be grounds for giving it a much greater role in drafting the drug safety claims on new product literature. In 1998, CDER issued 237 regulatory letters regarding prescription drug

promotions deemed to be false, misleading or unbalanced. This is probably not surprising. Both the scientists who have spent 3 or 4 years working on a drug and the marketing personnel whose job it is to promote that drug may be too close to the product to remain objective. By contrast, the pharmacovigilance function has the remit and the overarching view of research and development that is required to maintain an unbiased perspective.

4. Keeping the Regulators Happy

Signs that the regulators are keen to improve drug safety are already apparent. In May 1999, the FDA – stung by consumer criticism for approving five drugs which subsequently needed to be withdrawn from the market – announced plans to increase its postmarketing surveillance of new drugs and develop an active signalling system for identifying adverse effects.[7] The agency is also said to be considering whether to restrict the number and types of patients using a drug immediately after it wins approval.

The debate was taken further when it was suggested that the FDA could consider increasing the number of patients required for clinical trial databases. Alternatively, it could ask companies to conduct trials that reflect real life situations – with patients who, for example, have underlying diseases or taking concomitant medications. But even if the FDA does not demand such additional proofs of safety, it may well introduce tougher measures elsewhere, including faster production of reports.

Where the FDA leads, other regulators tend to follow. However, the impact of novel therapies and lifestyle drugs, shorter product lifecycles, increasing reliance on information technology and an ever more knowledgeable public demanding ever more disclosure could produce still more momentous changes – including the creation of a single global agency. If this happens, pharmacovigilance will assume an even greater importance; after all, failure to deliver the proofs of safety the regulator requires might then restrict sales of a drug or even block it from every market worldwide.

5. Conducting More Postmarketing Surveillance

But the focus of attention in pharmacovigilance – as it is in the regulatory agencies – is as much on what takes place once a drug has been launched as it is on getting it to market. This, too, is likely to become much more demanding.

Up to 80% of the workload generally follows market launch, largely because in the drug development process toxicity studies are primarily performed to satisfy regulatory requirements. In other words, they are conducted in relatively small, homogenous populations over relatively short time intervals and in relatively atypical conditions. However, it sometimes takes far longer to identify a problem. Indeed, it took 20 years to establish that aspirin (acetylsalicylic acid) increases the incidence of gastric ulcers[8] and many of the new drugs coming onto the market will prove even harder to evaluate. Some will be so highly specialised that the patient population on which they can be tested is too small to satisfy the normal criteria for clinical studies. Others will draw on new forms of medical knowledge such as genomics and proteomics.

Demographic changes and the development of lifestyle drugs will also increase the importance of postmarketing surveillance. With greater longevity and medications for conditions that were once beyond the industry's skill to treat, more people will take more drugs – and more combinations of drugs. In short, though clinical trials will always be important, the emphasis will shift to real-time reporting of outcomes data on drugs that have already been launched.

6. Moving Towards Real-Time Reporting

If it is to move towards real-time reporting, the pharmacovigilance team will need to set up regional centres for collecting adverse effects data from a variety of sources and report that information in electronic form to the regulatory agencies (figure 4). But in that case it also makes sense to collect data on pharmacogenomics and overall out-

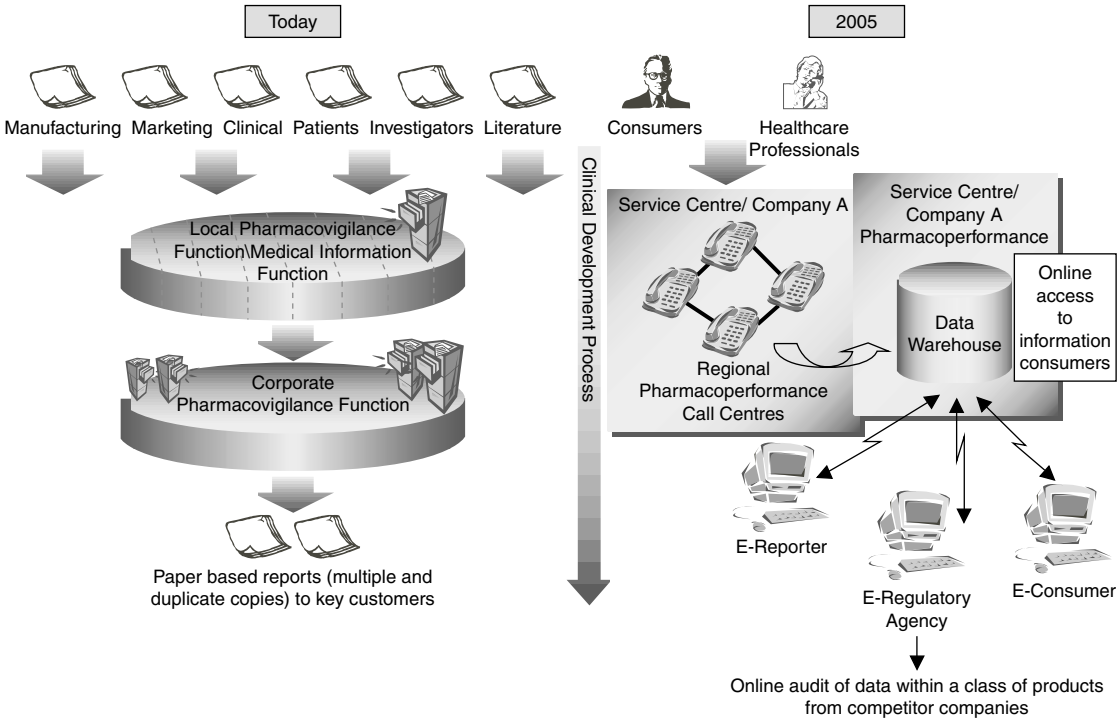

Fig. 4. Moving to a networked organisation.

comes, in order to assess a drug's performance and not just its safety.

Real-time reporting is what the leading agencies will soon expect. In 1998, CDER introduced a new information technology system for receiving the nearly 250 000 reports of suspected drug-related adverse events it gets every year. It is now encouraging pharmaceutical manufacturers to submit adverse event reports electronically. It is now only a matter of time before real-time reporting becomes mandatory, with periodic on-line audits by the agencies to ensure the integrity of the data.

7. Creating Standardised Global Systems

In fact, the changes the industry is now experiencing suggest that it will have to go very much further, with the creation of truly global pharmacovigilance operations. Both the increase in access to the Internet and the general trend towards globalisation mean that what happens in one market now has an impact worldwide.

There are other good reasons for setting up a global function with a standardised reporting system that spans differences in language, culture and geography. Uniformity of data collection, processing, evaluation and reporting removes the potential for disputes and misunderstandings. It also eliminates much of the need for rework, accelerates the speed with which a trial database can be finalised for submission to the regulators and makes it much easier to collate individual case reports into the periodic updates which the industry is required to provide. In addition, it enables a company to perform meta-analyses and to eliminate duplication of effort throughout the whole company.

8. Acquiring New Skills

What should be clear from this is the fact that the pharmacovigilance team of the future will fulfil a totally different role. It will not be a standalone department responsible for monitoring drug safety, but a global centre of knowledge intrinsic to the research and development operation as a whole. It will not be a paper-based archive buried deep in the organisation but the heart of an electronic network that includes clinical specialists, healthcare providers, the regulators and consumers.

A new role demands new skills. The people who help to shape the design, draft the guidelines and ensure the performance of the drugs we take will need to be much more proactive, much more strategic in their thinking and much more attuned to e-business. They will also need to adopt a global rather than a local or regional outlook in a world that is rapidly becoming one large marketplace.

But if the task is huge, so are the potential rewards. A company that can prove its drugs are both safe *and* effective beyond the rarefied environment of the laboratory will be able to command premium prices. It will also become the 'supplier of choice' for healthcare professionals and patients alike. Given fingertip access to megabytes of medical information, what 'e-educated' consumer will not favour pharmaceutical companies and products with an untarnished safety record?

Acknowledgements

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