

THE YIN AND YANG OF pharmaceutical companies

DARREN CHEW and ERIC M YOSHIDA look at the pros and cons of this powerful industry.



Some 50% of Ireland's exports are linked to pharmaceutical production, and Ireland is the second largest net exporter of medicines in the world.¹ According to the Industrial Development Agency (IDA) Ireland, the estimated replacement value of the Irish pharmaceutical sector is more than €40 billion. Furthermore, 20% of research and development in Ireland goes towards research and development of chemicals and chemical products.² However, the industry's research integrity and overall benefit to the public has constantly been questioned. Some argue that although newer drugs may be superior to existing ones, the exponential increase in prices imposes an unnecessary burden of expense. Others counter that the long-term benefits outweigh increasing costs, since even small improvements in current drugs can lead to scientific breakthroughs down the road. Compounding the controversial role of pharmaceutical companies are those of researchers and prescribing physicians – are they co-operative conspirators or consumer crusaders?

Pharmaceutical companies in the media

In the popular 1993 movie *The Fugitive*, Dr Richard Kimble (played by Harrison Ford) is framed for murder by employees of a pharmaceutical company because his research would eliminate any possibility of their drug acquiring FDA approval. While not as corrupt as Hollywood portrays them to be, pharmaceutical companies have had their fair share of scandals exposed in the public domain. One widely reported example was the market withdrawal of the then-popular cyclooxygenase-2 (COX-2) inhibitor agent, rofecoxib, under the brand name Vioxx (Merck & Co Inc, Whitehouse Station, NJ). With a budget of \$100 million allocated towards advertising per year, at one point the United States saw 10 million prescriptions of Vioxx written per month.³ After having been consumed by 80 million patients with a sales profit of \$2.5 billion in five years, the drug was withdrawn by Merck because the APPROVE study on colorectal adenoma prophylaxis demonstrated a 1.92-fold

increase in the relative risk of myocardial infarctions and strokes.⁴ Despite concerns by some physicians regarding the adverse effects of Vioxx, Merck-sponsored studies claimed the drug's cardiovascular safety.

Last year, it was reported that Pfizer, a large pharmaceutical company, paid \$2.3 billion to the United States federal and state governments in settlement of civil and criminal allegations that it had illegally marketed several drugs. In addition, another COX-2 inhibitor, Bextra (valdecoxib), encountered the same fate as Vioxx and was withdrawn by Pfizer in 2005.⁵ While Bextra could still provide relief for indications such as post-surgical pain, its lack of FDA approval for this particular use relegated its prescription for acute pain to off-label. Although off-label use is not illegal, Pfizer's sales representatives were allegedly directed by the company to promote the drug for treatment of acute and surgical pain at doses well above those approved by the FDA. John Kopchinski, a former Pfizer sales representative who was an initial complainant regarding the allegation, was quoted by the *New York Times* as saying: "The whole culture of Pfizer is driven by sales, and if you didn't sell drugs illegally, you were not seen as a team player".⁵ However, it was also revealed that the half dozen 'whistle-blowers' would share a Government bounty in excess of \$102 million.

Benefits of the pharmaceutical industry

Despite legitimate public concerns about pharmaceutical companies, it is clear that the industry, along with the manufacturers of medical devices and equipment, is necessary for medical progress. Without pharmaceutical-funded research and development, finding alternative financial resources to further clinical knowledge would be difficult.⁶ Relying solely on government funds to research, develop, manufacture and provide a means of distributing drugs to those in need has proven to be inadequate. In fact, this year the Irish Minister for Health and Children requested financial assistance from the pharmaceutical industry because of the recession.¹

Recently, regulations have been developed to maintain medical integrity and to address perceived deficiencies within the private sector. Unfortunately, well-publicised pharmaceutical scandals have diverted attention away from significant advances made by these companies, which produced revolutionary drugs and improved medical care.⁷ For instance, Pfizer also developed Lipitor (atorvastatin), which is currently the most prescribed drug worldwide.⁸ Atorvastatin, a HMG CoA reductase inhibitor, plays a critical role in treating patients with hyperlipidaemia by lowering cholesterol and preventing fatal cardiac events such as cerebrovascular accidents or myocardial infarctions.^{9,10} Furthermore, pharmaceutical companies have developed and manufactured antiviral agents to treat hepatitis B, hepatitis C and HIV – all of which, until recently, had no efficacious therapy.¹¹ Another example of the pharmaceutical industry's contribution to healthcare was Hoffman-La Roche's response to the call by politicians and scientists for a greater and faster production of oseltamivir (Tamiflu) to fight the H1N1 swine flu last year.¹²

There are several protocols in place to ensure that marketing practice provides accurate and unbiased information on drugs so that rational, evidence-based decisions can be made. These codes of behaviour are determined both by European law (legislation SI541 – Control of Advertising on Medicinal Products)¹³ and self-regulating Irish bodies (IPHA – the Irish Pharmaceutical Healthcare Association),¹⁴ of which all big pharmaceutical companies are members.

These provide specific codes of conduct to guarantee ethical behaviour and eliminate fringe benefits. For example, sales representatives may not give gifts for the personal benefit of healthcare professionals (clause 14.3 of the IPHA guidelines), and meetings cannot take place at venues that are known for entertainment or extravagance (clause 16.3).¹⁴ As part of marketing authorisation requirements for all pharmaceutical companies, all employees must obtain annual training on SI541 and the IPHA code of practice before they are certified to promote products to medical professionals.¹⁴ Furthermore, all commercial products and every word or design on them must have legal, medical and regulatory sign-off from the pharmaceutical company's internal committees, who in turn answer to the IPHA and SI541.

The Irish Medicines Board is the competent authority in Ireland and has the power to audit pharmaceutical companies to ensure that they are compliant with SI541 and other legislation to maintain their marketing authorisation licence.¹⁵ Written requests by doctors for drug samples are required, and only a maximum of six samples can be given to a doctor per year.¹⁴ The IPHA guidelines are becoming more stringent, in that starting next year, only four samples can be given to a doctor per year.¹⁶

Drug safety is also intensely regulated, and all potential pharmaceutical agents must successfully complete a series of registered clinical trials from phase I (demonstrating safety and determining dose ranges) to phase III (demonstrating both safety and efficacy) before obtaining licensure that allows marketing for a specific indication.¹⁷ During clinical trials, the pharmaceutical company follows strict protocols developed by the sponsor's medical officers and leading academic specialists in the field to determine patient eligibility requirements, schedule of tests, procedures, medications, dosages and length of

study. Numerous safety measures are taken to ensure the participants' protection. All registered clinical trials have an interim analysis conducted by an independent drug safety and monitoring board (DSMB) consisting of medical specialists in the particular area that are not directly involved in the clinical trial at hand.¹⁸ On the authority of the DSMB, a study can be terminated prematurely if the therapeutic arm of the study performs far superiorly or inferiorly than the control arm, or due to safety concerns. Participating centres must have the new protocols and any amendments that occur during the trial approved by an independent institutional review board (IRB), sometimes called a clinical research ethics board, before the study commences.¹⁹

The IRB consists of appointed medical specialists, nurses, social workers, statisticians and medical ethicists who act in the interest of the study participants. Every subject must give informed consent after being provided with a document written in lay language explaining the study protocol, rationale for the protocol, possible benefits of the study medications, possible adverse effects and, most importantly, that participation is entirely voluntary such that the patient may choose to withdraw from the study at any point. Patients are also protected by the Clinical Centre Patients' Bill of Rights, which ensures privacy, confidentiality and access to their medical records.²⁰

In addition, the United States public law and the FDA mandates that the sponsors or designated principal investigators register and report the results of clinical trials.¹⁴ Monitors are sent to verify that all protocol requirements are met; otherwise, the centre's data are disqualified, and the internal validity of the study suffers. In addition to drug contributions, pharmaceutical companies take the concept of corporate citizenship very seriously. For example, Pfizer is involved in several programmes that promote health without advertising their products. These include partnership in: 'pain proposal' – an EU document raising issues around the treatment and awareness of chronic pain; 'healthy heart campaigns' – a movement that raises awareness and provides nursing support for doctors involved in cardiac care; and, the 'quit with help' campaign – a drive that encourages smoking cessation in conjunction with organisations such as the Irish Cancer Society.¹⁶

The role of healthcare professionals

Government assistance and support from non-governmental organisations and philanthropic foundations is available for many aspects of basic science research, where a potential financial payout is not readily perceived. On the other hand, the progress of modern clinical medicine requires the entrepreneurial spirit of rival pharmaceutical companies as a driving force.

The incentive of market share and profit creates a willingness to invest in innovation, while a competitive environment ensures that only the best products make it to the market. Physician involvement in the pharmaceutical process is integral, whether success is defined by better patient outcomes or, from the perspective of the industry and its shareholders, enhanced market share and profitability. Development of pharmaceutical-sponsored clinical trials requires

medical specialists to define the endpoints of clinical trials, to develop the study protocols, to serve on a clinical trial's DSMB and to conduct the trials. Once licensure is achieved and the drug is ready for sale, pharmaceutical companies often create medical advisory boards to provide clinical advice on the product and its market.¹⁶ As such, physicians are in a position to ensure that the pharmaceutical process works in the best interests of patients and the medical profession.

Since the consumer of pharmaceutical products is often perceived to be the prescribing physician rather than the patient, physicians can exert substantial leverage in an industry that blurs the distinction between medical education and product marketing. Many major medical conferences use pharmaceutical sponsorship to fund the event, but physicians and medical students can reduce industry bias by insisting that sponsorship and funding of events be made through unrestricted educational grants.

However, this is difficult in reality, since funds are scarce.

Furthermore, physicians and medical students can be 'watchdogs' to alert appropriate government agencies, the media and the public if serious ethical or clinical breaches occur. Overall, one may argue that the benefits provided by the pharmaceutical industry outweigh deficiencies within the system, especially when the appropriate checks and balances, such as SI541 and the IPHA code of practice, are in place to protect the public interest. Whether in the form of education, programme implementation, economic stimulation or breakthrough drugs that improve life expectancy, it is evident that pharmaceutical companies contribute towards healthcare innovation and progress.

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