What can we learn from drug marketing efficiency?

The time it takes new drugs to penetrate the market is shrinking. David Kao suggests how drug companies’ techniques could be used to improve safety surveillance systems.

Institutions responsible for monitoring drug safety have been criticised widely after the withdrawal of drugs such as rofecoxib because of safety concerns. An estimated 20 million patients received prescriptions for rofecoxib over five years before the drug was withdrawn, and events attributable to rofecoxib may number in tens to hundreds of thousands. Regulatory bodies such as the US Food and Drug Administration have simultaneously been under pressure to reduce drug approval times to ensure timely availability of new drugs. However, concerns have been expressed that deadlines for approving drugs have reduced the focus on safety.

New efficiencies in drug marketing exacerbate the problem because rapid adoption of new drugs can quickly expose large numbers of patients to unknown risks. Here, I review trends in drug approval times in the United States, the mechanism by which this has been achieved, and concerns raised by this approach. I then discuss an example of the speed with which a new product may be adopted once approved and suggest improvements to drug safety surveillance systems.

Trends in drug approval

Faced with staffing and budget limitations on drug approval, the US Congress passed the Prescription Drug User Fee Act in 1992. This authorised the FDA to collect fees from drug manufacturers and use the revenue to hire additional staff to review drugs and improve its administrative infrastructure. In return, the FDA established goals of reviewing 90% of priority new drug applications within six months and 90% of standard new drug applications within 12 months. As a result, the mean review time in the US decreased from 33.6 months during 1979-86 to 16.1 months during 1997-2002. The act has been renewed three times since 1992, and revenues collected from industry now account for 43% of the FDA budget for drug oversight. Similarly, the European Agency for the Evaluation of Medicinal Products receives 75% of its funding in this manner, and the United Kingdom’s Medicines and Healthcare Products Regulatory Agency is entirely funded by user fees.

Critics have voiced concern over the dependence of regulatory agencies on drug companies for operational funding. Although drug approval times have decreased overall, the relation between this trend and subsequent postmarketing safety problems is less clear. Drug withdrawal rates have not increased overall since the US act, but a recent study showed that drugs approved in the US in the two months before the mandated deadline are more likely than those approved at other times to be withdrawn for safety reasons, to carry a subsequent black
Box warning, or to have at least one dosage voluntarily discontinued by the manufacturer. Because drugs approved more than three months before or just after the deadline were not associated with the same degree of subsequent safety problems, the authors concluded that the deadlines may increase the likelihood of unexpected safety problems. Deficits in postmarketing safety monitoring may, in turn, prevent these safety concerns from being discovered for years after approval. Depending on the success of the product, this can mean widespread exposure of patients to risk. Rapid acceptance of new products without concomitant improvements in postmarketing surveillance can only exacerbate this risk.

**Marketing motivations and methods**

The time required to bring a new product to market in the US has been decreasing for the past 20 years. For drug manufacturers, rapid deployment and adoption are necessary for cost recovery and to maintain market penetration in the United States. Because drugs approved more than three months before or just after the deadline were not associated with the same degree of subsequent safety problems, the deadlines may increase the likelihood of unexpected safety problems. Deficits in postmarketing safety monitoring may, in turn, prevent these safety concerns from being discovered for years after approval. Depending on the success of the product, this can mean widespread exposure of patients to risk. Rapid acceptance of new products without concomitant improvements in postmarketing surveillance can only exacerbate this risk.

**The balance between marketing and safety**

Drug marketing can be sophisticated and very successful. This is understandably desirable for manufacturers given the pressures of finite patent life and the imminent arrival of competitors. Kao expresses concern that successful marketing of new medicines, especially in the regulatory environment that allows a shorter lead time from submission to market access, might compromise patient safety. His description of sitagliptin’s market penetration in the United States is an impressive story from an industry perspective. It also raises the issues of drug industry involvement with disease awareness campaigns and patient organisations, as well as direct to consumer advertising as methods of promoting product awareness. A recent European Commission consultation focused on the role of industry in providing information on medicines to patients, and although there was overall agreement that the present ban on direct to consumer advertising should remain, there was perhaps predictable variation in stakeholders’ responses.

**Current systems**

Are safety systems up to the challenges posed by the more rapid arrival of new drugs in the marketplace? Public availability and independent scrutiny of safety data from clinical trials would be important but is not routine. Spontaneous report systems such as the US Adverse Events Reporting System, the WHO Collaborating Centre, and the UK Yellow Card are all valuable. Shortcomings such as lack of speed, biased reports, and lack of denominator data are well known, but important signals have been identified in this way. Sophisticated methods of interrogation, including disproportionality analysis and data mining techniques, have greatly enhanced the utility of these data.

In the UK the Drug Safety Research Unit runs a prescription event monitoring system that monitors safety through prospective cohort studies. Events rather than suspected adverse reactions are recorded prospectively in large cohorts of users in advance of any suspicion of toxicity. Record linkage systems such as the General Practitioner Research Database in the UK, PHARMO in the Netherlands, and many others across Europe provide a multipurpose platform on which to build comprehensive proactive drug surveillance. Because data are routinely collected from representative population samples, signals can be pursued and generalisable conclusions reached quickly once exposure starts to build and events are recorded.

**Unsuspected problems**

The concerns about methods for monitoring safety are relevant for all new drugs, not just those that might be rushed through the regulatory authorisation process. The potential safety issues cannot be fully known at the time of licensing and launch of any product, rushed or not, on simple statistical
a class is reflected by the decrease in time between approval of new class drugs and follow-on drugs over the past 30 years. Most drug classes now have at least one competitor in advanced stages of development at the time that the first drug in the class is approved, and more follow-on drugs are in development at the time that the first in the class is approved than ever before (figure). Furthermore, the mean and median interval of marketing exclusivity have decreased from highs of 8.2 and 10.2 years respectively (n=9 drugs) during the 1960s to 1.8 and 1.2 years from 1995-8 (n=18 drugs, P<0.0001 and P=0.0005, respectively).7 Once FDA approval is received, companies must act quickly to establish dominance before a competitor becomes available.

Recent years have seen major changes in drug marketing strategies facilitated by the evolution of mass media and prompted by changes in the relationships between manufacturers, doctors, and patients. Doctors are more aware of the effect of marketing on prescription practices, and concerns regarding conflicts of interest have led to changes in institutional policy in many settings, making traditional marketing to doctors more challenging.17 These changes have resulted in marketing budgets being moved to campaigns directed at funders and, where permitted, consumers.31 In countries such as the UK, where direct advertising to patients is prohibited, the public may still access internet resources designed for patients in other countries.

Public health initiatives regarding disease awareness and education have become important vehicles for increasing public demand for drugs, and engagement of healthcare funders is also a priority to ensure availability and coverage of costly new products for patients. The success of these strategies has been magnified by new mass media technologies, and companies are capitalising on their favourable cost-benefit ratio. This is exemplified by Merck’s discussion in their 2006 and 2007 annual business briefings of the efficiency of techniques such as video detailing and of their transition to multichannel marketing campaigns using web, video, and customisable, unbranded education resources to engage potential customers.11 These techniques enable drug companies to reach more potential customers faster than ever before. In most cases, this is not harmful and can benefit many patients in need of new treatment options. Nevertheless, improved infrastructure for postmarketing surveillance will be crucial to minimise risk to users of these new products.

Monitoring drug safety

Many groups have criticised the FDA for the time taken to publicise suspected risks associated with approved products like rofecoxib. As a result, the Federal Drug Administration Amendments Act of 2007 included a 50% increase in fees collected in association with the Prescription Drug Users Fee Act, with $291.2m designated specifically for surveillance of drug safety. FDA postmarket surveillance
ANALYSIS

relies heavily on the Adverse Event Reporting System, which collects spontaneous reports from manufacturers, providers, and consumers that are reviewed by scientists at the Center for Drug Evaluation and Research. This database is publicly available and updated quarterly, although it is difficult to extract meaningful datasets and the data are of variable quality. The World Health Organization Collaborating Centre for International Drug Monitoring, also called the Uppsala Monitoring Centre, integrates reports collected by similar systems in 83 member countries into a single database called Vigibase, which in June 2007 contained about 3.87 million cases.14 Vigibase is not publicly available, although it is possible to purchase extracts of this database for about $2500 (€1600) per drug entity and reports of analyses are sent periodically to member pharmacovigilance centers.

Most adverse event reporting systems rely on voluntary reporting of clinical observations and therefore are sensitive to many biases. Lack of associated data on usage also makes it difficult to determine the true frequency of adverse events identified, and observers have called for development of an active postmarketing surveillance system wherein cohorts of patients are followed after starting a new treatment.15 Surveillance system wherein cohorts of patients are followed after starting a new treatment.15 Surveillance system wherein cohorts of patients are followed after starting a new treatment.15

Emerging marketing techniques use several methods that might also be used to engage a wider audience in monitoring drug safety. The 2007 FDA Amendments Act includes some examples such as the requirement that television advertisements must instruct patients experiencing negative side effects to report their symptoms to the FDA.19 Other techniques might also prove useful. For example, public health initiatives sponsored by drug companies have helped providers to raise disease awareness. Expanding this collaboration to include campaigns dedicated to drug safety surveillance could provide healthcare professionals with the marketing expertise and infrastructure to track utilisation patterns. Merck has described a shift towards a “value based partnership” marketing model that builds product loyalty by rewarding customers with individual benefits in the form of convenience and improved health outcomes.17 Maximising the direct benefit to individual patients and providers from participating in a drug safety surveillance programmes might similarly increase voluntary involvement. Reporting a single adverse event provides little direct benefit to the reporting individual, but the development of tools for managing prescriptions, which in turn communicate with broad utilisation monitoring systems, provides patients and doctors with personal incentives to take an active role in drug safety monitoring by giving a useful service in return for their participation. A multifaceted approach to postmarketing surveillance of drug safety involving all stakeholders in healthcare including providers, payers, regulatory agencies, and patients seems likely to hold the most promise for maximising the benefits of pharmaceutical advancements while minimising unknown risks.

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Including all stakeholders in postmarketing surveillance of drug safety might be the way to prevent another rofecoxib

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