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Learning the Value of Drugs - Is Rofecoxib a Regulatory Success Story?

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Controversy over recent revelations concerning the adverse cardiovascular effects of selective cyclooxygenase-2 (COX-2) inhibitors has generally been framed as a story of regulatory failure, in which the Food and Drug Administration (FDA) has failed in its mission to protect the public from unsafe products. But this simplistic understanding of the mission of the FDA seems to make failure all but inevitable, if the reliable observation of the risks and benefits of a drug requires rigorous long-term studies. Perhaps in an earlier era the goal of drug regulation was simply to protect the public from poisons.[1] Today, drug regulation guides the development of information that turns poisons, used advisedly, into drugs. From this perspective, the growing knowledge of the complex effects of COX-2 inhibitors might be retold as a story of regulatory success.

Drugs are information-rich chemicals that in some respects resemble other information products (such as databases) more than they do other chemicals (such as industrial solvents). Information derived from rigorous testing distinguishes the chemicals we call "drugs" from similar chemicals sold for other purposes or even for the same purposes (such as minimally regulated dietary supplements). Creating new molecules has become relatively cheap, but determining their effects in patients has remained stubbornly expensive, time-consuming, and risky.[2] Moreover, the job is never finished. Years after a product has appeared on the market, further studies may reveal that it is useless or even toxic in patients with an indication for which it was once widely prescribed (e.g., hormone-replacement therapy for the prevention of heart disease in postmenopausal women) or, conversely, that a product once withdrawn because of toxic effects has unsuspected therapeutic benefits (e.g., thalidomide for leprosy). Information about drug effects is an extremely valuable resource for guiding both sound therapeutic choices and future product development.

Although we rely primarily on pharmaceutical firms to supply this information, we have reason to worry that, in an unregulated market, these firms would provide either too little information or distorted information. Getting profit-seeking companies to provide reliable information about the effects of drugs in patients is thus a major challenge for regulators.

One problem that is common to many markets for information products is that firms that produce the information may be unable to capture its value. Suppose a seller of unpatented dietary supplements believes that it could increase demand for its products by conducting clinical trials to convince skeptics that the products are safe and effective. At best, the seller would have to share this expanded market with competitors who did not pay for the trials. Facing this competition, it could not raise its prices, even though the tested product would be worth more to consumers than the untested product. The trials would look like a poor investment.

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Patents mitigate this problem by allowing firms to exclude competitors from the market and, thus, to set prices that reflect the enhanced value to consumers of the information-rich product — but only up to a point. As the end of the patent term approaches, a firm may find it hard to recover the costs of clinical trials by selling a product at a premium price before competition comes into play. Patents therefore do more to promote the early testing of new drugs than the further testing of old drugs. FDA-administered periods of market exclusivity sometimes provide additional motivation for testing old drugs.[3]

A more intractable problem is that firms have no way to capture the value of negative information. Clinical trials may increase demand if they show that a drug is safe and effective, but they will reduce demand if they show the opposite. The information is socially valuable either way, but the value of negative information accrues entirely to patients, insurers, and sellers of substitute products, rather than to the drug's manufacturer.

A recent case in point is rofecoxib (Vioxx). After receiving FDA approval in the late 1990s to market rofecoxib for the treatment of pain and inflammation associated with osteoarthritis, menstruation, and rheumatoid arthritis, Merck pursued additional trials of the drug for the prevention of recurrent colonic polyps. These trials confirmed previous indications that treatment with rofecoxib increases the risk of serious cardiovascular events.[4] This is lifesaving information that has considerable value to patients, doctors, scientists, insurers, and competitors. But from the viewpoint of Merck and its shareholders, the information destroyed value. This radical difference in perspective makes it imprudent to rely on the unfettered judgment of pharmaceutical firms to determine what we learn about the effects of drugs.

Firms face powerful incentives to develop and disclose information selectively, and perhaps even to delude themselves, in order to maximize sales. FDA regulation constrains these impulses by providing oversight of trial design, scrutiny of results by FDA scientists and outside experts, and assurance that marketing claims correspond to underlying data.[1] Consider, again, Merck's fateful decision to test rofecoxib for the prevention of recurrent colonic polyps. By this point, data from a prior study comparing rofecoxib with naproxen had suggested that cardiovascular risk was increased among patients taking rofecoxib. Although Merck optimistically attributed the difference to protective effects of naproxen rather than to toxic effects of rofecoxib, Merck scientists surely realized that further data could potentially support either hypothesis. Why would Merck take such a risk with a product that had sales of $2.5 billion a year?

Without dismissing the motivating power of scientific integrity and concern for public health, it seems likely that regulatory considerations fortified Merck's resolve to pursue further trials. Regulatory constraints on off-label marketing would limit available strategies for persuading doctors to prescribe (and insurers to pay for) an expensive drug like rofecoxib for prophylactic use without FDA approval, particularly in the face of questions about toxicity. A similar study was already under way of Pfizer's rival product, celecoxib (Celebrex), threatening to put Merck at a marketing disadvantage if celecoxib were approved for an indication that remained off-label for rofecoxib. FDA oversight also undoubtedly helped to persuade Merck that the cardiovascular effects of rofecoxib called for further study. Although the FDA has limited power to compel firms to conduct post-marketing studies, it must approve the labeling for drugs, and it has the authority to issue a public health advisory or even recall a product with adverse effects from the market, giving it some leverage with manufacturers.[1]

Recent newspaper accounts report that Merck marketing executives, reluctant to signal a lack of confidence in rofecoxib, opposed a study focused primarily on cardiovascular risks.[5] Instead, Merck decided, in consultation with the FDA, to monitor data on these risks in ongoing studies of new indications, thereby signaling optimism about new markets rather than concern about side effects. As more data came in, the FDA reached agreement with Merck to disclose the cardiovascular risks in the rofecoxib label in 2002.[4] Perhaps Merck hoped that rigorous long-term studies, culminating in the FDA's imprimatur on a supplemental new drug application, would put this concern to rest.

Some commentators have argued that the FDA should have required Merck to conduct trials designed primarily to evaluate cardiovascular toxic effects, rather than simply observing cardiovascular side effects in trials designed to prove efficacy for new indications.[4] Perhaps a regulatory process that gave a larger role in trial design to independent regulators, rather than leaving it largely to manufacturers, would generate more information about toxic effects at an earlier stage. But it is not obvious

that doing so would provide more valuable information more quickly than the system we have now.

Studies testing efficacy and safety are more informative than those testing safety alone; indeed, it is difficult to make sense of the concept of safety apart from the vantage point of particular patient populations and therapeutic goals. To rank safety ahead of efficacy seems to miss the obvious point that patients may be harmed by disease as well as by drugs. The challenge for physicians is to know which risks are worth taking for which patients — an evaluation that requires understanding benefits as well as risks. The challenge for regulators is to see that the necessary information is developed and disseminated appropriately and that marketing claims do not get ahead of the data. Only through well-informed advice can physicians minimize harm to patients.

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