Here is a challenge: Imagine you are asked to turn a new prescription drug into a blockbuster. The drug is approved by the US Food and Drug Administration (FDA) to treat arthritis pain. That is good news because the arthritis market is huge. But you face some big challenges. First, there are several over-the-counter drugs available that treat pain equally well and at one-fiftieth of the cost. Your only comparative advantage is that your drug causes less gastrointestinal tract (GI) bleeding than other arthritis pain medicines. But this reduction is not very big and only applies to a very small slice (probably <5%) of the market—people at high risk for GI bleeding. And, oh yes, your drug may triple the chance of myocardial infarction.

See also pages 1969, 1976 and 2024

Do you think you could get physicians to prescribe your drug to over 20 million Americans? Could you achieve over $2 billion in annual sales? Well, the makers of Vioxx (Merck & Co Inc, Whitehouse Station, New Jersey) did just that—until the drug was pulled from the market.

Ross et al show how a cumulative meta-analysis might have led the FDA to halt sales of Vioxx in 2001, 3 years before Merck voluntarily stopped selling it. Doing so might have prevented thousands of myocardial infarctions. We applaud this study and hope that independent investigators will apply the same methods to other drugs to help answer important safety questions. But the article left us wondering, just how did Vioxx get so big and stay so big for so long?

The Vioxx story really highlights the difference between marketing and informing. If physicians and patients had had the facts, it would have taken an alchemist, not a marketing department, to turn this lemon into gold.

The problem is that when it comes to prescription drugs, a lot more effort goes into marketing than informing. It has been estimated that drug companies spend $30 billion to $50 billion a year on drug promotion (advertising, detailing visits, free samples, and other promotion techniques). That means that the industry can really get its message out.

And marketing works. Physicians and patients are influenced by the enormous volume of commercial information that they receive. In this issue of the Archives, Weppner et al document that the familiar marketing tactics, long used in direct-to-consumer advertisements in maga-
zines and television, have made it to the Internet: company Web sites magnify perceived drug benefit, minimize perceived harms, and give out free samples. Although “free” might not be the right word, given the substantial costs of continuing these medications. Law et al, also in this issue of the Archives, describe a plausible link between drug advertising and increasing prescription costs.

In the face of so much marketing, where can physicians and patients find unbiased information? It turns out that there is a place where independent experts routinely critique the evidence supporting the use of prescription drugs: It’s the FDA. While the FDA has been criticized for being too close to industry, too quick or too slow in approving drugs, too politicized, too overworked, and too underfunded, it is nonetheless a gold mine of information. Food and Drug Administration reviews are a unique source of published and unpublished data about drug performance (search page available at http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm). And perhaps most importantly, readers can learn what the reviewers thought of the drugs they evaluated.

**THE VIOXX STORY**

What did the FDA reviewers have to say about Vioxx? In 1999, when the drug was first approved, the FDA’s take was clear: the drug was no more effective than other non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief of osteoarthritis. This was demonstrated in 2 six-week phase III trials against ibuprofen, 2 one-year trials against diclofenac sodium (where Vioxx was in fact statistically inferior), and 1 trial against naproxen in an elderly population (where neither drug was more effective than placebo). And the FDA was not convinced that Vioxx was safer, specifically rejecting the claim that Vioxx—unlike other NSAIDs—was not associated with upper GI toxic effects. In a safety review noted by Psaty in testimony before the US Senate, the FDA reviewer also expressed concern about possible cardiovascular harm: “With the available data, it is impossible to answer with complete certainty whether the risk of cardiovascular and thromboembolic events is increased in patients on rofecoxib. A larger database will be needed to answer this and other safety comparison questions.” At the same time, Merck was conducting an intense direct-to-consumer advertising campaign that helped create the mistaken impression that Vioxx was better and safer than other NSAIDS.

In early 2001, the FDA convened an advisory panel to review the findings from the newly completed VIGOR trial. Vioxx had a lower rate of severe GI bleeding than naproxen, and Merck wanted the FDA to remove its warning about GI toxic effects (included for all NSAIDs) from the label. The FDA rejected this argument. They were not convinced (1) that Vioxx was free of GI toxic effects, (2) that its safety advantage applied to the lower-risk general population, or (3) that fewer ulcer-related events translated into an overall safety benefit. In fact, they noted that NSAID-related toxic effects (involving liver and/or kidney function, hypertension, and edema) were consistently higher with Vioxx than with other NSAIDs.

Most importantly, the FDA wanted to add a warning to the label about the statistically significant increase in cardiovascular risk observed in the VIGOR trial. Despite reviewer concerns, the original label made no mention of this possible harm.) Merck argued against the warning, asserting that Vioxx did not increase cardiovascular risk but that naproxen lowered it. The FDA rejected this argument, citing the lack of any prior studies documenting cardioprotection with naproxen, the implausible effect size (which exceeded aspirin’s benefit over placebo in reducing cardiovascular events), and the consistently high rates of myocardial infarction compared with NSAIDS in 3 other studies it reviewed.

Under FDA regulations, the prescription drug label is written by the drug’s manufacturer and approved by the FDA after negotiation. From the public’s perspective, the negotiation did not go so well. It took over a year to change the label to include data about cardiovascular risk. And rather than putting the change in the “warning” section of the label, the cardiovascular concerns were relegated to the less prominent “precautions” section and were said to be of unknown clinical significance.

Had the message—that Vioxx was no more effective than other NSAIDS, had a GI safety advantage only for people at especially high risk for bleeding, and tripled the chance of myocardial infarction compared with naproxen—been effectively delivered, Vioxx sales would likely have plummeted. Instead they increased.

**MAKING INFORMATION AVAILABLE**

To make good treatment decisions, physicians and their patients need unbiased information about the benefits and harms of interventions. It would be naive to expect the pharmaceutical industry—or any seller—to provide unbiased facts. Spin is intrinsic to marketing. So it is no surprise that magnifying benefit and minimizing harm can be found wherever drugs are sold: drug company Web sites, direct-to-physician advertisements, and of course, direct-to-consumer advertisements.

Physicians and patients should be able to get credible, unbiased information directly from the FDA—not through the filter of industry. For this to happen, the FDA needs to make what its reviewers know more accessible. The FDA should create standardized executive summaries of drug reviews that quantify the benefit and important harms found in the phase III trials. We developed a possible format for presenting these data, called the prescription drug facts box, modeled on the FDA’s nutrition facts boxes. We have shown in 2 national randomized trials that most consumers can understand and use the data tables.

The summaries should also highlight remaining uncertainties—such as reviewers’ concerns about the cardiovascular harms of Vioxx—and routinely mention whenever the FDA requires postmarketing studies (ie, phase IV studies). Physicians and patients should know about the existence of such studies, why they were needed, and what their status is.

But it will take a lot of work to keep this information from being drowned in the sea of industry marketing. It’s
a pretty deep sea. Merck spent $500 million promoting Vioxx in 2003 alone—an amount equal to the FDA's total annual budget for all human drugs. One key strategy is widespread dissemination. Summaries should be posted on the FDA Web site, attached to prescription drug labels, required on direct-to-consumer advertising, published in medical journals, and reprinted in popular professional electronic resources. It's time for the FDA to bring its information to the market.

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