

ble, and it would reduce rather than increase public expenditures. Well-targeted federally funded medication trials can more than pay for themselves; examples to date include NIH-supported studies of estrogen replacement and of medications for hypertension, which provided important insights into the risks, benefits, and optimal use of these therapies. These needed insights can improve care and save the nation billions in drug expenditures.⁵ For instance, if a moderate-size NIH-funded clinical trial of the cardiovascular risks of coxibs had been performed in 2000 and 2001, most of the \$2.5 billion per year — about \$1 billion annually from public coffers — that was spent on rofecoxib (Vioxx) might have been saved. Other clinical examples abound.

The torcetrapib story suggests that we have become too dependent on manufacturers as the predominant source of our scientific knowledge about the effects of medications. As Medicare prepares for an increasingly unaffordable drug benefit, the best way to contain that public expenditure will be to commit a small fraction of those funds to support such public-interest drug trials, fairly comparing

competing therapies (especially costly new ones) with clinically realistic alternatives. With pharmaceutical costs increasing faster than most other health care expenditures, the nation requires studies that will meet the needs of evidence-based prescribing and not just the needs of the pharmaceutical industry. It is not a question of whether we can afford to pay for our own drug trials; it is increasingly evident that we cannot afford not to do so.

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The Lessons of Vioxx — Drug Safety and Sales

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On November 23, 2000, the results of the Vioxx Gastrointestinal Outcomes Research study, known as VIGOR, were published in the *Journal*. This randomized, controlled trial showed that rofecoxib, an inhibitor of cyclooxygenase-2 that had been marketed as Vioxx since May 1999, was associated with fewer gastrointestinal complications than naproxen, a standard nonsteroidal antiinflammatory drug. Unexpectedly, the VIGOR study also showed that the patients who were given rofecoxib had four times as many myocardial infarctions as those who were given naproxen.

This finding of a significant increase in the risk of myocardial infarction was an early signal of a potentially serious safety problem with rofecoxib. Nonetheless, sales remained robust. By the time of rofecoxib's withdrawal from the market in September 2004, after a placebo-controlled study confirmed its cardiovascular risk, more than 100 million pre-

scriptions had been filled in the United States.¹ Tens of millions of these prescriptions were written for persons who had a low or very low risk of gastrointestinal problems.²

On May 5, 2005, the Government Reform Committee of the U.S. House of Representatives, on which I serve as the senior Democrat, held a hearing that explored how drugs with serious safety issues, such as rofecoxib, can remain so popular for so long. What we learned illuminated a hidden corner of the health care system: the practices that pharmaceutical manufacturers use to promote their products to physicians.

The pharmaceutical industry spends more than \$5.5 billion to promote drugs to doctors each year — more than what all U.S. medical schools spend to educate medical students. Major drug companies employ about 90,000 sales representatives — one for every 4.7 doctors in the United States, according to the American Medical Association.³ Although substantial marketing expenditures are common

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in many industries, the potential effect of drug marketing on health raises special concerns. For years, the industry has justified these expenditures on the grounds that they fund essential education for doctors. According to the Web site of the Pharmaceutical Manufacturers and Research Association, “many physicians learn about new drugs — indeed, about ongoing research in their areas of specialization — largely through information provided by the companies that market new products.” But if the primary goal is sales, not education, and the information provided to physicians is slanted or misleading, the health consequences for patients can be serious.

Because of the recent events surrounding rofecoxib, the May 5 hearing of the Government Reform Committee focused on Merck, the manufacturer of Vioxx, which has an excellent reputation within the drug industry and supports many products, such as vaccines, that are medically essential but not very profitable. The company funded VIGOR and appropriately sought to publish its results in a prestigious medical journal. In advance of the committee’s hearing, Merck cooperated voluntarily with our request for information, providing more than 20,000 pages of internal company documents. Merck also voluntarily sent a senior executive to testify at the hearing and answer the committee’s questions. Yet as we learned, even a company like Merck can direct its sales force to provide clinicians with a distorted picture of the relevant scientific evidence.

On February 7, 2001, the Arthritis Drugs Advisory Committee of the Food and Drug Administration (FDA) met to discuss the VIGOR study. At this meeting, Merck argued that the significant increase in the rate of myocardial infarction (which further analysis had determined to be a fivefold increase) was explained by a protective effect of naproxen, not by any inherent risk posed by its drug. After the FDA’s medical reviewer and others expressed concern about this explanation, the advisory committee voted unanimously that physicians should be made aware of VIGOR’s cardiovascular results.

The next day, Merck sent a bulletin to its rofecoxib sales force of more than 3000 representatives. The bulletin ordered, “DO NOT INITIATE DISCUSSIONS ON THE FDA ARTHRITIS ADVISORY COMMITTEE . . . OR THE RESULTS OF THE . . . VIGOR STUDY.” It advised that if a physician inquired about VIGOR, the sales representative should indicate that the study showed a gastroin-

testinal benefit and then say, “I cannot discuss the study with you.”

Merck further instructed its representatives to show those doctors who asked whether rofecoxib caused myocardial infarction a pamphlet called “The Cardiovascular Card.” This pamphlet, prepared by Merck’s marketing department, indicated that rofecoxib was associated with 1/8 the mortality from cardiovascular causes of that found with other antiinflammatory drugs.

The Cardiovascular Card provided a misleading picture of the evidence on rofecoxib. The card did not include any data from the VIGOR study. Instead, it presented a pooled analysis of preapproval studies, in most of which low doses of rofecoxib were used for a short time. None of these studies were designed to assess cardiovascular safety, and none included adjudication of cardiovascular events. In fact, FDA experts had publicly expressed “serious concerns” to the agency’s advisory committee about using the preapproval studies as evidence of the drug’s cardiovascular safety.⁴

Persistent physicians who sought additional information about the cardiovascular effects of rofecoxib were directed to send inquiries to the company’s headquarters. Merck’s response to these physicians highlighted the misleading information from the Cardiovascular Card.

Beyond these specific communications to physicians, our committee also heard evidence of a broad disparity between the evidence-based perspective provided by scientific journals and expert committees, on the one hand, and the sales pitch used by the company’s field staff, on the other. Merck instructed its sales representatives, for example, to provide only certain approved study results to doctors. Approved scientific studies were defined as those that provide “solid evidence as to why [doctors] should prescribe Merck products for their appropriate patients.” By contrast, those studies that raised safety questions about drugs were considered background studies. Distributing the results of a background study was “a clear violation of Company Policy.”

Merck also trained its representatives to identify speakers for educational events who were “opinion leaders” who could provide “favorable” views of the company’s products to other doctors. Underlining the promotional nature of these events, Merck instructed its sales representatives to track whether the physicians who attended them subsequently prescribed more Merck drugs.

In addition to providing selective evidence and biased presentations, Merck counseled its representatives to use an array of subliminal selling techniques to affect prescribing — potentially undermining the ability of physicians to choose drugs strictly on the basis of the risks, benefits, and costs for a particular patient. For example, in a training course on selling skills, Merck taught representatives to mimic the words and body language of doctors during sales calls. The curriculum explained that “mirroring is the matching of patterns, verbal and non-verbal, with the intention of helping you enter the customer’s world. It is positioning yourself to match the person talking. It subconsciously raises his/her level of trust by building a bridge of similarity.”⁵

The committee hearing raised serious questions about the marketing practices used by Merck, but it would be a mistake to restrict the lessons learned to a single company. The testimony we heard indicated that Merck’s marketing practices may be less aggressive and more ethical than those of many of its competitors. What is needed is a broad assessment of the ways in which all new drugs are promoted and prescribed in the United States.

As a policymaker, I see a need to enhance the FDA’s resources, authority, and oversight of new drugs. The agency does not review all industry promotional material (such as the Cardiovascular Card) quickly; it should have the resources to do so and the authority to require review before dissemination. The FDA should also have more authority to ensure that key information is promptly incorporated into drug labels, and warn doctors about potential safety risks. In the case of a drug such as

rofecoxib for which there are serious outstanding concerns about safety, the agency should have the authority to restrict advertising until these concerns have been adequately addressed by further research.

Legislative reform will not be successful, however, without attention to this issue in hospitals and doctors’ offices. All the Merck documents discussed above, and many others, are available on our committee’s Web site.⁵ Practicing physicians, journal editors, and leaders of associations of medical professionals may find these documents useful as they develop new strategies to keep promotional efforts from distorting clinical care.

As we move forward, it is important to recognize that physicians, drug manufacturers, regulators, and policymakers all share the same goal: realizing the vast potential of safe and effective new drugs for improving the health of Americans. We all share responsibility for ensuring that important evidence translates into sound medical practice.

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Tailoring Arthritis Therapy in the Wake of the NSAID Crisis

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In recent months, physicians and patients have been presented with a confusing array of decisions by the Food and Drug Administration (FDA) and the pharmaceutical industry regarding the use of non-steroidal antiinflammatory drugs (NSAIDs): Merck

withdrew its cyclooxygenase-2 (COX-2) inhibitor, rofecoxib, from the market; a closely divided FDA advisory panel recommended continuing the marketing of rofecoxib and other COX-2 inhibitors; and the FDA has requested that Pfizer suspend sales of valdecoxib in the U.S. market, contrary to the recommendation of its advisory committee (although Pfizer is planning discussions with the

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