PERSPECTIVE

Failing the Public Health — Rofecoxib, Merck, and the FDA

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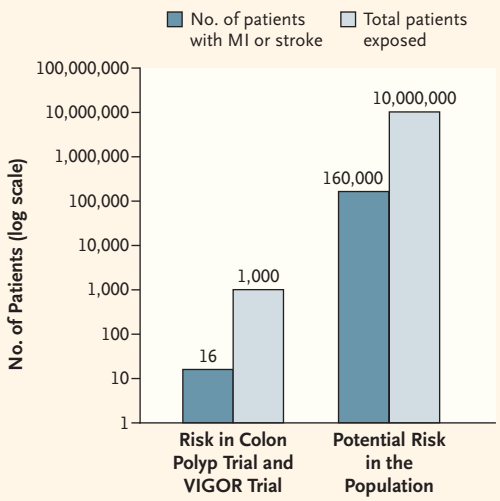
On May 21, 1999, Merck was granted approval by the Food and Drug Administration (FDA) to market rofecoxib (Vioxx). On September 30, 2004, after more than 80 million patients had taken this medicine and annual sales had topped $2.5 billion, the company withdrew the drug because of an excess risk of myocardial infarctions and strokes. This represents the largest prescription-drug withdrawal in history, but had the many warning signs along the way been heeded, such a debacle could have been prevented.

Neither of the two major forces in this five-and-a-half-year affair — neither Merck nor the FDA — fulfilled its responsibilities to the public. The pivotal trial for rofecoxib involved 8076 patients with rheumatoid arthritis and demonstrated that this coxib had lower gastrointestinal toxicity than naproxen.[1] Even though the drug was approved in 1999 on the basis of data submitted to the FDA, the data were not submitted to a peer-reviewed journal until the following year and did not appear in print until November 23, 2000, one and a half years after commercial approval had been granted. The cardiovascular data reported in that article were incomplete, in part because of incomplete ascertainment: the design and execution of the trial had not anticipated that untoward cardiovascular events might occur.[1]

It was not until February 8, 2001, that the FDA Arthritis Advisory Committee met to discuss concern about the potential cardiovascular risks associated with rofecoxib. It remains unclear why the FDA waited two years after its review and approval of rofecoxib to conduct this meeting. My colleagues and I reviewed the data from the meeting that were made publicly accessible and published an analysis of all the available data on rofecoxib and celecoxib on August 22, 2001.[2] Our primary conclusion, based on the clear-cut excess number of myocardial infarctions associated with rofecoxib and the numerical, albeit not statistically significant, excess associated with celecoxib, was that "it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents."[2] Such a trial needed to be conducted in patients with established coronary artery disease, who frequently have coexisting osteoarthritis requiring medication and have the highest risk of further cardiovascular events. Given the very high coincidence of coronary disease and arthritis, this group may represent the largest segment of the population for whom rofecoxib was prescribed. In light of the insight that arterial inflammation is the basis for myocardial infarction and stroke and the knowledge that coxibs reduce the production of biomarkers of inflammation such as C-reactive protein and improve endothelial function, such a trial would also have been quite attractive from the standpoint of potential benefit. The trial would have prospectively determined the incidence of cardiovascular events, whose possible association with coxib treatment had not been anticipated in the early and pivotal trials of these drugs.

Unfortunately, such a trial was never done. The FDA has the authority to mandate that a trial be conducted, but it never took the initiative. Instead of conducting such a trial at any point — and especially after the FDA advisory committee meeting in 2001 — Merck issued a relentless series of publications, beginning with a press release on May 22, 2001, entitled "Merck Reconfirms Favorable Cardiovascular Safety of Vioxx" and complemented by numerous papers in peer-reviewed medical literature by Merck employees and their consultants. The company sponsored countless continuing medical "education" symposiums at national meetings in an effort to debunk the concern about adverse cardiovascular effects. The message that was duly re-



Risk of Myocardial Infarction (MI) or Stroke Associated with Rofecoxib Use.

Data are from Mukherjee et al.[2] and the Adenomatous Polyp Prevention on Vioxx (APPROVe) study.

inforced was that rofecoxib had no cardiovascular toxicity: rather, naproxen was cardioprotective. Only by happenstance, in a trial involving 2600 patients with colon polyps who could not have been enrolled if they had had any cardiovascular disease, was it discovered that 3.5 percent of the patients assigned to rofecoxib had myocardial infarction or stroke, as compared with 1.9 percent of the patients assigned to placebo ($P<0.001$), necessitating premature cessation of the trial and the decision to discontinue treatment with rofecoxib.

Over the course of the five-and-a-half-year saga, many epidemiologic studies confirmed and amplified the concern about the risk of myocardial infarction and serious cardiovascular events associated with rofecoxib.[3] These studies considered large populations, up to 1.4 million patients, tracking the use of various nonsteroidal antiinflammatory medications or coxibs to determine the risk of adverse events. Each time a study was presented or published, there was a predictable and repetitive response from Merck, which claimed that the study was flawed and that only randomized, controlled trials were suitable for determining whether there was any risk. But if Merck would not initiate an appropriate trial and the FDA did not ask them to do so, how would the truth ever be known?

Meanwhile, Merck was spending more than $100 million per year in direct-to-consumer advertising — another activity regulated by the FDA and a critical mechanism in building the "blockbuster" status of a drug with annual sales of more than $1 billion. For the past few years, every month has seen more than 10 million prescriptions for rofecoxib written in the United States alone. At any point, the FDA could have stopped Merck from using direct-to-consumer advertising, especially given the background concern that the cardiovascular toxicity was real and was receiving considerable confirmation in multiple studies conducted by investigators who were independent of Merck. The only significant action taken by the FDA occurred on April 11, 2002, when the agency instructed Merck to include certain precautions about cardiovascular risks in its package insert. The FDA also sponsored one of the large epidemiologic studies performed in a cohort of Kaiser Permanente patients.

Considering the tens of millions of patients who were taking rofecoxib, we are dealing with an enormous public health issue. Even a fraction of a percent excess in the rate of serious cardiovascular events would translate into thousands of affected people. Given the finding in the colon-polyp trial in low-risk patients without known cardiovascular disease — an excess of 16 myocardial infarctions or strokes per 1000 patients — there may be tens of thousands of patients who have had major adverse events attributable to rofecoxib (see Figure).

I believe that there should be a full Congressional review of this case. The senior executives at Merck and the leadership at the FDA share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health. Sadly, it is clear to me that Merck's commercial interest in rofecoxib sales exceeded its concern about the drug's potential cardiovascular toxicity. Had the company not valued sales over safety, a suitable trial could have been initiated rapidly at a fraction of the cost of Merck's direct-to-consumer advertising campaign. Despite the best efforts of many investigators to conduct and publish meaningful independent research concerning the cardiovascular toxicity of rofecoxib, only the FDA is given the authority to act. In my view, the FDA's passive position of waiting for data to accrue is not acceptable, given the strong signals that there was a problem and the vast number of patients who were being exposed. Furthermore, the tradeoff here involved a drug for symptoms of arthritis, for which many alternative medications are available, in the

context of serious, life-threatening cardiovascular complications. Certainly there are many facts that we are not privy to, such as the direct communication between the FDA and Merck, but all the facts can and should be scrutinized closely in a Congressional review in order to avert such a catastrophe in the future.

From the Cleveland Clinic Foundation, Cleveland.

1. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8.
2. Mukherjee DM, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954-9.
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Coxibs and Cardiovascular Disease

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The coxibs are a subclass of nonsteroidal anti-inflammatory drugs (NSAIDs) designed to inhibit it selectively cyclooxygenase-2 (COX-2).[1] Their development was based on the hypothesis that COX-2 was the source of prostaglandins E_2 and I_2, which mediate inflammation, and that cyclooxygenase-1 (COX-1) was the source of the same prostaglandins in gastric epithelium, where they afford cytoprotection. Three coxibs — celecoxib, rofecoxib, and valdecoxib — have been approved for use by the Food and Drug Administration (FDA); a fourth, etoricoxib, has been approved by the European regulatory authority, and it and a fifth, lumiracoxib, are currently under consideration for FDA approval.

Coxibs have been aggressively marketed directly to consumers in the United States and have rapidly dominated the prescription-drug market for NSAIDs, accounting for worldwide sales of roughly $10 billion. Rofecoxib has now been withdrawn from the market by Merck, following the premature cessation, by the data and safety monitoring board, of the Adenomatous Polyp Prevention on Vioxx (APPROVe) study, which was designed to determine the drug's effect on benign sporadic colonic adenomas. This action was taken because of a significant increase by a factor of 3.9 in the incidence of serious thromboembolic adverse events in the group receiving 25 mg of rofecoxib per day as compared with the placebo group. Blood pressure was elevated in patients in the rofecoxib group early in the course of the study, but the incidence of myocardial infarction and thrombotic stroke in the two groups began to diverge progressively after a year or more of treatment.

Coincident with the approval of rofecoxib and celecoxib in 1999, my colleagues and I reported that both drugs suppressed the formation of prostaglandin I_2 in healthy volunteers.[2] Prostaglandin I_2 had previously been shown to be the predominant cyclooxygenase product in endothelium, inhibiting platelet aggregation, causing vasodilatation, and preventing the proliferation of vascular smooth-muscle cells in vitro. However, it was assumed that prostaglandin I_2 was derived mainly from COX-1, the only cyclooxygenase species expressed constitutively in endothelial cells. This assumption later proved incorrect, since studies in mice and humans showed that COX-2 was the dominant source. The individual cardiovascular effects of prostaglandin I_2 in vitro contrast with those of thromboxane A_2, the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction, and vascular proliferation.

Whereas aspirin and traditional NSAIDs inhibit both thromboxane A_2 and prostaglandin I_2, the coxibs leave thromboxane A_2 generation unaffected, reflecting the absence of COX-2 in platelets. Increasing laminar shear stress in vitro increases the expression of the gene for COX-2, leading our group to suggest that COX-2 might be hemodynamically induced in endothelial cells in vivo. If so, suppression of the COX-2–dependent formation of prostaglandin I_2 by the coxibs might predispose patients to myocardial infarction or thrombotic stroke.

Thus, a single mechanism, depression of prostaglandin I_2 formation, might be expected to elevate blood pressure, accelerate atherogenesis, and predispose patients receiving coxibs to an exaggerated thrombotic response to the rupture of an atherosclerotic plaque. The higher a patient's intrin-