



## The Vioxx Fallout

By John E. Calfee

*The drug Vioxx, used to treat arthritis and other forms of chronic pain, has been the focus of two dramatic events in the past year and extensive criticism in the press. The first event was the decision of its maker, pharmaceutical giant Merck and Co., to withdraw it from the market; the second was a Texas verdict that held Merck liable for millions in damages because of the death of a man who had taken the drug regularly for several months. Both Vioxx and the other drugs in its subclass, known as Cox-2 inhibitors, are now viewed with very great suspicion. The irony is that the past year has also seen important new research findings and a thorough reassessment of older research, indicating that these drugs have many important benefits and great potential for addressing serious problems including cancer—without posing undue risks to patients.*

On September 30, 2004, pharmaceutical manufacturer Merck and Co., acting alone without consulting the Food and Drug Administration (FDA), withdrew its pain reliever Vioxx (rofecoxib) from the United States and all other markets after a three-year clinical trial revealed significantly more adverse cardiovascular events (heart attacks and strokes) among Vioxx users. Although the possible cardiovascular effects of Vioxx had already been widely discussed in the medical literature and occasionally in the popular press, Merck's action was a shock: the firm's market capitalization dropped 27 percent on the day Vioxx was withdrawn. (At the closing of the market on August 18, 2005, one day before the Texas court verdict discussed below, Merck stock was trading at 30 percent below its price on the day before the Vioxx withdrawal. On September 26, Merck closed at 27.83, 38 percent below the closing price on September 29, 2004.)<sup>1</sup>

Both Merck and the FDA immediately came under widespread criticism for suppressing earlier clinical data and failing to withdraw Vioxx years

before. The debate rapidly extended to other drugs in the same class, which at the time included Celebrex and Bextra (respectively, celecoxib and valdecoxib, both marketed by Pfizer) in the United States, along with Prexige (lumiracoxib, marketed by Novartis), which was approved in the United Kingdom in October 2003 but has still not been offered for sale.

### The Cox-2 Class of NSAIDs

The Vioxx episode had its origins in a drug-safety problem that had plagued medicine since long before Vioxx was developed. Vioxx is a member of the class of drugs known as Cox-2 inhibitors. The Cox-2s are part of the larger class of NSAIDs (nonsteroidal anti-inflammatory drugs), which includes such popular pain relievers as Alleve (naproxen), Advil (ibuprofen), and several prescription-only drugs, along with the original NSAID, aspirin. The traditional NSAIDs are probably the most-used category of drugs worldwide, but they often cause upper gastrointestinal (GI) ulcers and bleeding. This can cause pain and even death. The most reliable estimate of the death toll from NSAID use in the United States

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is between ten and twenty thousand deaths annually (Wolfe, Lichtenstein, and Singh 1999). Many patients, especially elderly ones, must trade off the severe side-effects of NSAIDs against the pain and disability that safer pain relievers could theoretically prevent.

Some fifteen years ago, researchers discovered that NSAIDs suppress both the Cox-1 enzyme, which is protective of the stomach and the rest of the GI system, and the Cox-2 enzyme, which reinforces inflammation and thus causes pain (Whittle 2000). This insight suggested that a drug that selectively suppressed the Cox-2 enzyme could offer pain relief with less GI harm. Drug development based on this idea was swift. Pfizer's Celebrex was approved by the FDA on December 31, 1998 (new drug approvals are a common New Year's Eve event at the FDA), while Merck's Vioxx was approved five months later (and was followed in November 2001 by Bextra from Pfizer). Both were approved only as pain relievers, not as ulcer preventatives.

Vioxx and Celebrex became two of the fastest selling new drugs in history. In the meantime, Merck and Pfizer mounted additional clinical trials to demonstrate GI protection and to test the Cox-2s inhibitors' ability to prevent cancer and inflammation-related conditions such as Alzheimer's disease. In addition, other manufacturers ran trials for Cox-2s that have not yet been submitted for approval in the United States.

## **Vioxx, Cox-2s, and Cardiovascular Risk**

The biological processes triggered by NSAIDs are sufficiently strong and complex to suggest both increases or decreases in risk, with the exact effect possibly differing among specific drugs (FitzGerald and Patrono 2001; Mukherjee, Nissen, and Topol 2001; Bennett et al. 2005). (One NSAID, aspirin, has been demonstrated to prevent heart attacks and their recurrence; hence in this paper references to NSAIDs will generally mean non-aspirin NSAIDs.) When FDA staffers noted small signs of higher-than-normal occurrence of cardiovascular problems among Vioxx users during the pre-market review of Vioxx, they commented that this seemed typical of NSAIDs (Pelayo 1999). This remark proved to be prescient of the entire Vioxx affair.

In 2000, Merck released the results of the VIGOR trial, which demonstrated significant reductions in severe GI side-effects. However, Vioxx users encountered about twice as many serious cardiovascular events as patients taking naproxen, an older NSAID sold over

the counter as Aleve (Bombardier et al. 2000). The implications of these results were far from clear, however. The trial had not used a placebo control. Because cardiovascular events were not a pre-defined focus of examination, the ad hoc analysis generated on the basis of that study can legitimately yield only hypotheses rather than conclusions. For example, a significant elevation of cardiovascular events was noted only for patients for whom aspirin was indicated but not used. In contrast to VIGOR, earlier, smaller placebo-controlled trials had, if anything, suggested a reduced risk from Vioxx. Overall mortality in these trials, including VIGOR, and the subsequent APPROVe trial, a large-scale three-year placebo-controlled study of Vioxx to prevent the recurrence of colorectal polyps (a precursor to cancer), was not higher for Vioxx users. An obvious possibility was that naproxen, the drug taken by non-Vioxx users in VIGOR, may be cardioprotective.

The VIGOR results were widely discussed and debated in the medical community. The research literature quickly produced re-analyses of earlier trials along with new epidemiological studies (i.e., studies that do not randomly assign Vioxx and non-Vioxx users to different groups, which is normally essential to assess causation). Some of this research suggested a cardioprotective role for naproxen. Thus an editorial in the *Archives of Internal Medicine*, accompanying three studies of NSAIDs, concluded, "The findings in the VIGOR study . . . are readily explicable by the beneficial effects of naproxen rather than a detrimental effect of Cox-2 inhibitors" (Dalen 2002).

Several Cox-2 and NSAID reviews published during this period (Bjarnason, Takeuchi, and Simpson 2003; Whittle 2003; Dalen 2002) all reached roughly the same set of conclusions: The Cox-2s provided important GI protection. Most trials had not revealed significant cardiovascular problems, but at least one large trial (VIGOR) had. The VIGOR results might have been caused by a cardioprotective property of naproxen, but Vioxx itself might also have been the problem. Cardiovascular side-effects should be monitored. Essentially the same views were incorporated in the periodic updating of practice guidelines issued by professional organizations and practitioner-oriented journals (e.g., American Pain Society 2002; American Geriatrics Society 2002; American College of Rheumatology treatment guidelines in Schnitzer 2002).

Some critics urged Merck to mount a large clinical trial to assess cardiovascular risk, presumably against a

placebo (Mukherjee, Nissen, and Topol 2001). Such a proposal raised difficult questions. Should a trial examine patients with high risk for heart attacks and strokes (whose multiple drug use would greatly complicate the trial) or some other population? How many trials would be needed, given that trials with sufficient power to detect a small long-term risk would involve thousands of patients spread across scores or hundreds of medical practices and would require one to three years for design, execution, and analysis? Why study Vioxx at all, in view of the fact that much less was known about the risks of older NSAIDs? This issue proved moot when Merck included a tally of adverse cardiovascular events in APPROVe.

In April 2002, the FDA added a cardiovascular warning to Vioxx along with language supporting modest GI protection (but without removing the standard NSAID ulcer warning). Sales of Vioxx and of Cox-2s as a group reflected these evolving circumstances. After their extraordinary start, Cox-2 sales were essentially flat in 2001 through 2004 as the medical profession digested the VIGOR results and the subsequent debate.

## Cox-2s and NSAID Research

Probably the least appreciated side of the Vioxx–Cox-2 story pertains to other research. After the first Cox-2s were approved, Merck and other manufacturers proceeded with new large-scale trials, many of them exploring the tantalizing possibilities that Cox-2s could prevent serious conditions, including certain cancers.

The fact that the Cox-2 enzyme is involved in cancer opened up a new line of research into cancer prevention and treatment (Chau and Cunningham 2002). In addition, inflammation, which of course is suppressed by NSAIDs, has been identified as important in coronary heart disease, Alzheimer's disease, and diabetes. But by the 1990s, almost all NSAIDs were old drugs with little or no patent protection. This left scant incentive for manufacturers to invest in new research and development. The National Institutes of Health and other nonprofits did little to fill the gap.

This situation was transformed by the arrival of the Cox-2s. Indeed, most of what we know about both positive and negative long-term effects of NSAIDs comes from research on just this one subclass. It was one of the cancer prevention trials (APPROVe) that eventually caused Vioxx to be pulled from the market.

## The Vioxx Withdrawal and a Firestorm of Criticism

On September 23, 2004, just two months before APPROVe was scheduled to end, Merck was informed by the trial's review board that the Vioxx branch of the trial revealed a statistically significant increase in heart attacks and other adverse cardiovascular events such as strokes (Bresalier et al. 2005). After a week's discussion among a very small group of top-level executives, Merck withdrew Vioxx from all markets worldwide without consulting the FDA. It did so because Vioxx appeared unique among Cox-2s in its cardiovascular risk profile (Merck 2004). This appearance proved to be largely unfounded.

A storm of criticism immediately descended upon both Merck and the FDA for not having taken various actions including the withdrawal of Vioxx months or years earlier (e.g., Topol 2004b; *Lancet* 2004). Among the critics were leading medical journals and academic medical researchers, newspaper editorialists and op-ed writers, and participants in congressional hearings. A prominent Cleveland Clinic researcher, for example, published an op-ed entitled "Good Riddance to a Bad Drug" (Topol 2004a).

Most critics argued that Merck and the FDA had ignored the evidence on cardiovascular risks, failed to launch timely risk assessment trials, and failed to provide sufficient warnings, and that Merck went too far in promoting the drug to patients who lacked significant GI risk. Criticism rapidly encompassed all the Cox-2s and even other NSAIDs as a series of often contradictory studies suggested problems with Celebrex or naproxen or perhaps cardioprotection from Celebrex. A prominent theme was that the FDA had relaxed drug-safety standards and developed an inappropriately close relationship with the industry it regulates.

Throughout, the FDA's own view was relatively simple. A few weeks after Vioxx was pulled, acting deputy commissioner Janet Woodcock pointed out that "at this point we don't have any definitive evidence" that Cox-2s are riskier than traditional NSAIDs such as ibuprofen and naproxen" (Pollack 2004). There seems little reason to believe the FDA itself would have asked Merck to pull Vioxx from the market after APPROVe.

## February 2005—The Turning Point

The rapid evolution of scientific and medical appraisals of Vioxx and other NSAIDs reached a turning point in February 2005. On February 16–18, the FDA convened a

joint meeting of its advisory committees on arthritis and on drug safety and risk management.<sup>2</sup> The members unanimously concluded that cardiovascular risk was a class effect—that is, likely to afflict all Cox-2s to some degree. By an overwhelming 31 to 1 margin, the panel voted in favor of keeping Celebrex on the market. By a close vote (17 to 13 with 2 abstentions), it favored keeping Bextra on the market, and by a similarly narrow margin (17 to 15), voted in favor of permitting Vioxx back on the market. In each case the panel recommended the FDA's strongest warnings ("black box" warnings) about cardiovascular risk, along with "other measures" to limit the drugs' use. The panel also recommended new warnings for traditional NSAIDs, physician caution in prescribing traditional NSAIDs, and FDA caution in approving both new Cox-2s and new NSAIDs (Okie 2005; Kuehn 2005).

A consistent theme was the fear on the part of both committee members and FDA staff that traditional NSAIDs could prove at least as dangerous as Cox-2s, that the Cox-2 trials were our sole source of information on long-term NSAID usage, and that it was important to begin trials for the long-neglected older drugs (many of which are also somewhat selective in their action against Cox-1 versus Cox-2 enzymes).

## Recent Developments

On April 6, 2005, the FDA released a staff memorandum analyzing NSAID risks (Jenkins and Seligman 2005). The memo concluded that (1) all three FDA-approved Cox-2s (including Vioxx) are "associated" with an increased risk of serious cardiovascular events compared with a placebo, but it is impossible to rank the three drugs in terms of risk; (2) clinical trial data comparing Cox-2s with traditional NSAIDs do not "clearly demonstrate" that Cox-2s involve a greater cardiovascular risk than do traditional NSAIDs; (3) existing long-term placebo-controlled clinical trial data for traditional NSAIDs are inadequate for assessing the cardiovascular risk of traditional NSAIDs; (4) existing data are "best interpreted" as indicating a class effect of increased cardiovascular risk for both Cox-2 and traditional NSAIDs; and (5) short-term Cox-2 use for pain relief, particularly at low doses, "does not appear" to involve cardiovascular risk.

The FDA thus concluded that what had started as a Vioxx cardiovascular safety episode turned out to be a broader NSAID cardiovascular issue. Essentially all the contentious topics triggered by the VIGOR and

APPROVe trial results were now seen as issues for NSAIDs generally, not just Vioxx and not even just Cox-2s. The memo specifically recommended comprehensive analysis of existing data on cardiovascular risks and the launching of long-term controlled clinical trials of traditional NSAIDs.

The FDA staff memo also concluded that all Cox-2s probably reduce ulcer risk, but only Vioxx demonstrated reductions in serious GI bleeding. It also concluded that Bextra was unique among Cox-2s in causing a rare, serious skin reaction, rendering Bextra's risk-benefit profile "unfavorable for marketing."

The FDA immediately issued a Public Health Advisory on cardiovascular risks from all non-aspirin NSAIDs and recommended the addition of "black box" label warnings for cardiovascular risks and GI bleeding for all prescription non-aspirin NSAIDs, selective and non-selective alike. The FDA also asked Pfizer to withdraw Bextra from the market, leaving Celebrex as the only Cox-2 marketed in the United States (FDA 2005).

The European Medicines Agency, the European Union's primary pharmaceutical regulation agency, essentially tracked the February and April FDA findings and decisions. So did Health Canada, which regulates pharmaceuticals in Canada.

In July, Health Canada convened an expert panel on Cox-2 safety (Health Canada 2005). Among its remarkable results was an eleven to one vote to restore Vioxx to the market and a unanimous vote to keep Celebrex available. The report also supported the benefits of Cox-2s for many patients.

The events of February and April seem to have had remarkably little impact on the news media and the elite medical journals whose earlier criticisms these events had largely undermined. Our Nexis searches and examination of the relevant literature have thus far failed to discover overt repudiation or substantial alteration of the views so vigorously pronounced through academic and popular editorials in the months after Vioxx's withdrawal.

## The Role of Advertising

Although commentators often assume that direct-to-consumer (DTC) advertising played a large role in the uptake of Cox-2s, the evidence is surprisingly slender. Total Cox-2 DTC advertising in the year 2003 was \$165 million (Ives 2004) compared to sales of \$5.3 billion (IMS Health, 2005). Such a small advertising-to-sales ratio suggests limited returns to advertising. The

Cox-2s achieved rapid success in Canada (where NSAID prescriptions increased by 50 percent), in the United Kingdom (where Celebrex was the fastest-selling new drug in recent history) and in Australia (where Cox-2 sales caused a financial crisis in the health care system), all despite the complete absence of consumer advertising (Mamdani, Rochon, Laupacis, and Anderson 2002; Emery, Hawkey, and Moore 2001; Dowden 2003). Substantial Cox-2 usage beyond patients at high risk for upper GI problems was probably unavoidable. Patients taking traditional NSAIDs often encounter serious GI bleeding, even patients with little prior history of it (hence the practice guides that recommended Cox-2s as first-line therapies). Taken only once or twice daily, Cox-2s are easier to use than traditional NSAIDs and require less co-therapy for ulcer prevention. For some patients, Cox-2s may provide superior pain relief. All this made Cox-2s attractive to the great majority of patients who faced modest co-payments. Canadian and Australian studies found that most Cox-2s were prescribed to patients with little evidence of GI risk (Kerr et al. 2003; Mamdani, Rochon, Laupacis, and Anderson 2002).

Oddly enough, advertising was strongly limited in its ability to target Cox-2 usage. FDA rules prohibited manufacturers from promoting the GI benefits of Cox-2s because GI protection was never on the FDA-approved Celebrex label, and even after the APPROVe trial, Merck still had to warn patients of GI risks.

## The Merck Litigation

After Vioxx was pulled from the market, what had been a trickle of lawsuits over Vioxx safety became a torrent. By the middle of August 2005, nearly 5,000 cases had been filed, including about 150 putative class actions (*Wall Street Journal* 2005). The first to go to trial, *Ernst v. Merck*, concluded on August 19 when the jury awarded approximately a quarter billion dollars to the widow of a man who died after taking Vioxx for eight months. (The award must be reduced to about \$26 million because of a Texas law capping punitive damages.) The next trial is scheduled for September 12 in an Atlantic City, New Jersey, state court.

The *Ernst* case appears to be typical in charging that Merck heavily promoted Vioxx while failing to warn physicians and patients about cardiovascular side-effects. Another charge is that Merck was negligent in failing to mount more clinical trials of cardiovascular safety.

These allegations basically ignore what has been learned since September 2004. Had Merck offered vigorous cardiovascular warnings in the wake of VIGOR, it is far from clear that patients would have been safer if they had switched to traditional pain relievers. Even if we assume that Vioxx involved a modest increase in risk (at least among long-term users of the highest dose), it is hard to imagine how juries could identify the relatively few heart attacks actually caused by Vioxx given persistent findings in the medical literature that roughly half of heart attacks occur among patients with no identifiable risk factors (Braunwald 1997). In the *Ernst* case, there was no evidence that the patient died of a heart attack at all. (He died of heart arrhythmia, which has not been linked to Vioxx in clinical trials.) Post-verdict interviews suggest the jury simply ignored scientific testimony for the defense on causation.

Vioxx litigation promises to reflect public attitudes toward the pharmaceutical industry as well as toward Merck itself. At least one prominent newspaper editorialized that the Vioxx award served a useful purpose (“because this case was less about science than about punishing Merck”) despite the fact that the case relied upon “an extremely flimsy scientific basis” (*New York Times* 2005). Should that attitude continue to prevail in the face of what has been learned since September 30, 2004, Vioxx litigation could become very large.

The Merck litigation is extremely important. Its effects could dwarf those of previous litigation explosions. Unlike the subjects of other prominent pharmaceutical litigation, such as fen-phen, Vioxx is a drug whose continued use has been endorsed by several expert committees. Because the typical lawsuit seeks damages for behavior that for the most part was perfectly consistent with FDA regulations and policies, successful litigation would almost certainly force the FDA to revise its policies and standards with effects that would range far beyond this particular product or the classes to which it belongs. Pharmaceutical manufacturers would be substantially deterred from aggressively developing and marketing other drugs for chronic conditions (which are arguably the most valuable drugs we have). And of course, the effect of this litigation on Merck, a leading research firm, could be highly destructive.

## Vioxx and the FDA

The common argument that the FDA should have moved rapidly to force Vioxx off the market or require

vigorous warnings and/or large-scale clinical trials has proved largely unfounded. The quicker addition of a cardiovascular warning to the Vioxx label could have impeded rather than buttressed best clinical practices because the FDA eventually concluded that there is no compelling evidence that other Cox-2s or other NSAIDs are significantly safer than Vioxx (with the possible exception of the highest Vioxx dose). The same reasoning suggests it would have been a mistake for the FDA to have forced Vioxx off the market because of the VIGOR findings.

The FDA has long been criticized by economists and others for being too cautious in approving new drugs. If the FDA staff is too slow to approve a new drug, almost no one notices because few people know enough to assess what patients have been losing. If a drug gets approved and then runs into safety problems, public awareness is widespread and quickly expanded through the news media and other sources.

Some FDA critics have cited the Vioxx episode as evidence that the FDA now pays too little attention to safety because a substantial proportion of FDA funding comes from industry user fees (e.g., Topol 2004b). The user-fee legislation simply requires the FDA to make decisions faster, however, not to make decisions more favorable to the industry. At any rate, the Vioxx episode makes clear that the incentives for FDA staff to maintain drug safety standards at reasonable or higher-than-reasonable levels remains largely undisturbed. The fusillade of criticism directed at the agency over Vioxx and Cox-2s—especially from its most reliable base of support, the academic medical community and the most prestigious medical journals—vastly exceeds any criticism it has received in recent years for being too slow to approve new drugs or too quick to remove them. The Vioxx episode has made it more difficult for the FDA to do its job without tilting toward excessive caution in drug regulation.

The FDA has begun to require more warnings, especially the “black box” warnings that can dominate prescribing information (Harris 2005). An example is the April 11 imposition of black box warnings on seven anti-psychotic drugs (Mathews and Tesoriero 2005). Over-warning can impede useful prescribing, as many believe happened in the wake of new black box warnings on antidepressants. The FDA has also moved aggressively to make emerging clinical trial data available to physicians and the general public via the agency’s Drug Watch Web page. Undigested clinical trial results

can be highly misleading in terms of apparent drug benefits as well as drug side-effects, and also in generating unjustified litigation and inappropriate switches to older (and less safe) drugs.

Finally, there is the strong possibility that the FDA is moving toward even greater caution in approving new drugs and in the requirements it imposes on the clinical trials necessary to gain marketing approval. Certainly, this prospect is being widely discussed in the drug development community.

## The Fallout

Vioxx will probably return to the market unless litigation overwhelms Merck itself. Much of the initial criticism of Merck and the FDA has proved excessive if not unfounded. The advent of Cox-2 inhibitors including Vioxx has turned out to be extremely valuable both for their health benefits and for their contribution to what is known about the risks and benefits of NSAIDs generally.

Nonetheless, the Vioxx episode has already had a substantial adverse impact on Merck (which has another Cox-2 drug, Arcoxia, or etoricoxib, in advanced clinical trials); on other manufacturers of existing Cox-2s (some already approved in Europe) and Cox-2s under development;<sup>3</sup> on Cox-2 research for numerous conditions ranging from arthritis pain to cancer, cardiovascular disease, and Alzheimer’s disease; on the regulation of drug safety; on the FDA as an institution; and on the drug development and approval process for all drugs (not just NSAIDs or Cox-2s). Litigation will make all these negative trends far more destructive unless the courts begin to recognize the science that has been revealed in the eleven months since Vioxx was withdrawn.

## Notes

1. A few topics in this article are treated in greater detail in John E. Calfee, “The Roles of FDA and Pharmaceutical Companies in Ensuring the Safety of Approved Drugs, Like Vioxx,” on May 5, 2005, to the House Committee on Government Reform, available at [www.aei.org/publication22465](http://www.aei.org/publication22465); and John E. Calfee and Ximena Pinell, “The Significance of the Vioxx Withdrawal,” (working paper prepared for a conference on Consumers, Information, and the Evolving Healthcare Market Place, Cornell University, New York, April 6, 2005), available at [www.aei.org/publication23257](http://www.aei.org/publication23257).

2. Materials from the FDA Joint Meeting with the Drug Safety and Risk Management Advisory Committee, February

16–18, 2005, are available at [www.fda.gov/ohrms/dockets/ac/cder05.html#DrugSafetyRiskMgmt](http://www.fda.gov/ohrms/dockets/ac/cder05.html#DrugSafetyRiskMgmt).

3. Prexige (lumiracoxib, marketed by Novartis) was approved in the United Kingdom in October 2003, but Novartis has not placed the drug on the market pending EU approval, according to Jeanne Whalen, “Novartis Weighs Cap on Prexige Use,” *Wall Street Journal*, February 7, 2005.

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