

Vioxx, Cox-2s and NSAIDs: A Backgrounder

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The voluntary withdrawal of the pain reliever Vioxx by Merck on September 30, 2004 precipitated intense public interest in a larger class of drugs known as Cox-2 inhibitors or simply “Cox-2s,” and soon thereafter, in the even larger class known as non-steroidal anti-inflammatory drugs or NSAIDs. These include such popular over-the-counter drugs as ibuprofen (often sold under the brand names Advil and Motrin) and naproxen (often sold as Alleve) and several prescription-only drugs, plus the original NSAID, aspirin. All these drugs are effective pain relievers, especially for conditions like arthritis where inflammation plays a role. The recent \$254 million verdict in *Ernst v. Merck*, a lawsuit brought in Texas, ensures that all these drugs will remain in the public eye for some time. This backgrounder reflects, of course, my own assessment of the research literature and events at the FDA and elsewhere.¹

The Cox-2 Class of NSAIDs

Older NSAIDs, the ones used before the Cox-2s arrived, are often referred to as traditional NSAIDs. The traditional NSAIDs are probably the most-used of any drug category worldwide, but they often cause upper gastro-intestinal (G.I.) 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 is between ten and twenty thousand deaths

¹ This backgrounder is largely drawn from a forthcoming “Health Policy Outlook” to be published by AEI. My May 5, 2005 Congressional testimony, listed in the references, treats some topics not discussed here.

annually (Wolfe, Lichtenstein, and Singh 1999). Many patients, especially elderly ones, had to endure considerable pain and disability in order to avoid the severe side-effects of NSAIDs.

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 G.I. system, and the Cox-2 enzyme, which reinforces inflammation and thus causes pain (Whittle 2000). This insight suggested that a drug that selectively suppresses the Cox-2 enzyme could offer pain relief with less G.I. harm. Drug development based on this idea was swift. Pfizer's Celebrex (celecoxib) 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 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 G.I. protection and to test the Cox-2s' ability to prevent cancer and inflammation-related conditions such as Alzheimers. In addition, other manufacturers ran trials for Cox-2s that have not yet been submitted for approval in the U.S.

Vioxx, Cox-2s and Cardiovascular Risk

In theory, the biological processes triggered by NSAIDs could either increase or decrease the risk of heart attacks and strokes (often referred to as cardiovascular events; see 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 excess cardiovascular events among Vioxx users during their pre-market review, they commented that this seemed typical of NSAIDs (Pelayo 1999).

In the VIGOR trial, the results of which were published in 2000, Vioxx users encountered about twice as many serious cardiovascular events as patients taking

naproxen (Bombardier 2000). The implications of these results were unclear, however. The trial had not used a placebo control. Because cardiovascular events were not a pre-defined endpoint, *ad hoc* analysis of the data generated hypotheses rather than conclusions. For example, only the group of patients for whom aspirin was indicated to prevent heart attacks actually encountered a significant elevation of cardiovascular events. In contrast to VIGOR, earlier, smaller placebo-controlled trials had, if anything, suggested a reduced risk from Vioxx. Overall mortality in these trials, and indeed in the APPROVe trial itself, was not higher for Vioxx users. An obvious possible explanation for the VIGOR results was that naproxen, the drug taken by non-Vioxx users, may be cardio-protective.

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 G.I. 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 Geriatric Society 2002; American College of Rheumatology treatment guidelines in Schnitzer 2002).

In the meantime, Merck and other Cox-2 manufacturers proceeded with new large-scale trials, many of them exploring the tantalizing possibilities (discussed below) that Cox-2s could prevent serious conditions including certain cancers. 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, however, when Merck included a cardiovascular endpoint in APPROVe, a large-scale three-year placebo-controlled study of Vioxx to prevent the recurrence of colorectal polyps (a precursor to cancer).

In April 2002, the FDA added a cardiovascular warning to the Vioxx label along with language supporting modest G.I. protection (but without removing the standard NSAID warning about ulcers and G.I. bleeding). Vioxx and overall Cox-2 sales reflected this entire train of events. 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.

The Vioxx Withdrawal

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 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 was apparently unique

among Cox-2s in its cardiovascular risk profile (Merck 2004). This assumption proved to be largely mistaken.

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 2004a; *Lancet*, Dec. 4, 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 2004b).

Most critics argued that Merck and the FDA had ignored the evidence on cardiovascular risks, failed to launch timely risks assessment trials and provide sufficient warnings, and that Merck over-promoted the drug to patients without significant G.I. 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 cardio-protection 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” (*New York Times*, October 19, 2004). There seems little reason to believe the FDA itself would have asked Merck to pull Vioxx from the market after APPROVe.

The February 2005 FDA Meetings and Actions

On February 16-18, 2005, the FDA convened a joint meeting of its Arthritis and Drug Safety and Risk Management Advisory Committees.² The members unanimously concluded that cardiovascular risk was a class effect, i.e., likely to afflict all Cox-2s to

² Materials are available online at www.fda.gov/ohrms/dockets/ac/cder05.html#DrugSafetyRiskMgmt.

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 2005c; 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 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 vs 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 order 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; (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 an NSAID cardiovascular issue. The memo 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 that only Vioxx had been demonstrated to reduce serious G.I. bleeding. Finally, the memo 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 for *all* non-aspirin NSAIDs and recommended the addition of "black box" warnings for cardiovascular risks and G.I. bleeding to the labels of all prescription non-aspirin NSAIDs including Cox-2s as well as traditional NSAIDs. The FDA also asked Pfizer to withdraw Bextra from the market, leaving Celebrex as the only Cox-2 marketed in the United States.

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

In July, Health Canada convened an expert panel on Cox-2 safety (Health Canada 2005). The panel voted eleven to one to restore Vioxx to the market and voted unanimously to keep Celebrex available. The report also supported the benefits of Cox-2s for many patients and noted, as had the FDA, that cardiovascular risks for Cox-2s seemed comparable to those of the most popular traditional NSAIDs.

The Role of Advertising

Total Cox-2 direct-to-consumer (DTC) advertising in the year 2003 was \$165 million (*New York Times* Dec. 21, 2004) compared to sales of \$4.4 billion (IMS Health, IMS National Sales Perspectives). 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%), in the U.K. (where it was the fastest selling new drug in recent history) and in Australia (where it caused a financial crisis)—despite

comprehensive bans on consumer advertising in all these nations (Mamdani, Rochon, Laupacis, and Anderson 2002; Emery, Hawkey, and Moore 2001; Dowden 2003).

Substantial Cox-2 usage beyond patients at high risk for upper G.I. problems was probably unavoidable. Patients often encounter serious G.I. bleeding with little prior history (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. Cox-2s were therefore attractive to the great majority of patients who faced modest co-pays. Canadian and Australian studies found that most Cox-2s were prescribed to patients with little evidence of G.I. 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 G.I. benefits of Cox-2s because G.I. protection was never on the FDA-approved Celebrex label, and even after the APPROVe trial, Merck still had to warn patients of G.I. risks.

Cox-2s and NSAID Research

The NSAIDs are important not just because they are so widely used. It turns out that the Cox-2 enzyme is also involved in cancer. This fact 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, Alzheimers, 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 R&D. NIH and other non-profits 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 that eventually caused Vioxx to be pulled from the market.

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*, August 30, 2005). The first to go to trial, *Ernst vs 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.

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.

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