

CASE STUDY

The VIOXX Saga

A Case Study Against
Product Liability Reform Legislation

By Stephen G. Schwarz

On September 30, 2004, pharmaceutical giant Merck pulled the plug on its blockbuster arthritis drug Vioxx. The company announced that the data from a recent trial intended to show the benefits of Vioxx for patients with a history of colon polyps had instead shown a significant increased risk of stroke and heart attack in people taking Vioxx for 18 months as compared to those taking a placebo¹. Merck claimed that in putting the safety of patients first it had decided to withdraw Vioxx from the market even before the FDA ordered it to do so. Should Merck be commended for its selfless act of corporate responsibility forgoing significant additional profits to further the cause of patient safety? A thorough analysis of the Vioxx saga is far from flattering to Merck. In fact, this story has become the "poster child" for the upcoming fight against a Bush Administration tort reform proposal that would give companies like Merck immunity from suit where, as here, the drug had FDA approval.

Vioxx and the Advent of COX-2 Inhibitor Drugs

Non-steroidal anti-inflammatory drugs ("NSAIDs") such as aspirin, ibuprofen (Advil) and naproxen (Aleve) have been on the market and sold over the counter for many years. As their name suggests, these drugs are used to reduce inflammation, and thereby, reduce the pain caused by inflammation. Older established NSAIDs are non-specific inhibitors of the enzymes cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), meaning that they slow the production of these enzymes and thereby inhibit the function that these enzymes are designed to perform in the body. COX-2 has been more directly implicated in the production of inflammation and resulting pain, whereas the inhibition of COX-1 has been related to adverse gastrointestinal effects such as dyspepsia and bleeding of the GI tract. COX-1 prostaglandins (a group of fatty acid

● Stephen G. Schwarz is the managing partner in the Rochester, N.Y., law firm of Faraci & Lange. He is a past president of the Rochester Chapter of the American Board of Trial Advocates. His article, "Yet another medical malpractice insurance crisis," appeared in the Summer 2003 issue of VOIR DIRE.

derivatives found in many tissues in the body) protect the gastric lining. Hence, when NSAIDs inhibit COX-1 in some people this leads to damage to the gastric lining and bleeding (ulcers). For this reason, selective COX-2 inhibitors were believed to be a breakthrough in treating inflammation without causing the side effects on the GI tract that non-selective NSAIDs cause. Vioxx, Celebrex and Bextra are all COX-2 inhibitor drugs.

Even before the COX-2 inhibitors hit the market, it was known, or at least theorized, that these drugs would likely have another effect on the delicate chemical balance within the body's blood clotting system by increasing the tendency to form clots in arteries. This phenomenon, called a "prothrombotic" effect, was theoretically attributed to the ability of COX-2 drugs to alter the

favors prostaglandin formation over thromboxane formation. As one researcher I spoke with put it – Vioxx and the other COX-2 inhibitors are the "anti-aspirin." Most people are familiar with the use of aspirin in patients with cardiovascular risks. When taking aspirin, a patient's blood is less likely to clot in an artery and cause a blockage, known as a thrombosis. It was believed even before Vioxx was approved that COX-2s would have the opposite effect – enhancing and promoting the formation of thrombotic blockages. What was not known was whether this enhancement would be significant enough to cause adverse outcomes in patients taking the medication.

FDA Approval and the VIGOR study

On May 21, 1999, the FDA gave Merck approval to begin marketing Vioxx. The

FROM THE DATE OF THE PUBLICATION OF THE VIGOR STUDY FORWARD, BATTLE LINES WERE DRAWN IN THE MEDICAL LITERATURE BETWEEN THE TEAM OF MERCK SCIENTISTS AND THEIR SPONSORED CONSULTANTS IN ACADEMIA AND INDEPENDENT PHYSICIANS AND SCIENTISTS WHO CALLED FOR MORE RESEARCH TO PROVE THAT VIOXX WAS SAFE.

metabolism of arachidonic acid to favor thromboxane formation over prostaglandin formation. Although that may sound complicated, there is actually a very simple way to understand this effect – it is the precise opposite effect from the one that aspirin causes, which

basis of this approval was a trial of 8,076 patients with rheumatoid arthritis (referred to as the VIGOR study) comparing Vioxx to an over the counter NSAID naproxen sold under the trade name Aleve. The purpose of the VIGOR study was to see if Vioxx would achieve, in a

large trial, a reduction in gastrointestinal side effects by inhibiting COX-2 without inhibiting COX-1. In fact, the VIGOR study did demonstrate that Vioxx had a lower risk of gastrointestinal toxicity from long term use than did naproxen. However, the study also demonstrated something Merck had not counted on – that patients who took Vioxx suffered a significantly elevated risk of heart attack and stroke compared to those taking naproxen. The increase was not subtle either. Five times as many heart attacks and strokes occurred in the group of patients taking Vioxx (also generically called "rofecoxib") than in the group taking naproxen.

The results of the VIGOR study were submitted to the FDA in 1999 and were part of the data package utilized to obtain FDA approval. However, the data were not submitted to a peer-reviewed journal until the following year and the results were not published until Nov. 23, 2000, when the Bombadier, et al., article was published in the *New England Journal of Medicine*ⁱⁱ. The researchers who published the results of the VIGOR trial were sponsored or directly employed by Merck, including Dr. Alice Reicin. In commenting on the drastic difference in cardiovascular risk between the group taking Vioxx as compared to the group taking naproxen the authors stated that "our results are consistent with the theory that naproxen has a coronary protective effect and highlight the fact that rofecoxib [Vioxx] does not provide this type of protection owing to its selective inhibition of cyclooxygenase-2..." However, they also admitted that this theory "needs further confirmation in a larger study."

The Medical Literature Battle

From the date of the publication of the VIGOR study forward, battle lines were drawn in the medical literature between the team of Merck scientists and their sponsored consultants in academia and independent physicians and scientists who called for more research to prove that Vioxx was safe. One such independent researcher and Vioxx critic

was Dr. Eric Topol, a cardiologist at the Cleveland Clinic. Topol and his colleagues reviewed all of the data presented to the FDA on both rofecoxib (Vioxx) and celecoxib (Celebrex) and in August of 2001 published an analysis concluding that there was a clear-cut excess number of myocardial infarctions (heart attacks) associated with Vioxx and a numerical, although not statistically significant excess associated with Celebrex. The Topol group concluded that "it is mandatory to conduct a trial specifically assessing cardiovascular risk and benefit of these agents."ⁱⁱⁱ

A study published by Ray, et al., in 2002^{iv} approached the issue from an epidemiological standpoint. Up to that point, all trials of the selective COX-2 inhibitor drugs had been run on populations with low cardiovascular risk. Dr. Ray and his colleagues at Vanderbilt University looked into the cardiovascular history of people who had taken Vioxx, including those with pre-existing cardiovascular disease. In this group, Ray reported that the risk of heart attack was actually eight times higher than the already increased risk in the trial populations (11.6 heart attacks per thousand v. 1.45 heart attacks per thousand patient

had indicated should be done and which Topol and his group at the Cleveland Clinic had demanded, Merck took another tack. As Dr. Topol wrote in a commentary in the *New England Journal of Medicine* published in October of 2004^v:

Merck issued a relentless series of publications, beginning with a press release in May 22, 2001, entitled "Merck Reconfirms Favorable Cardiovascular Safety of Vioxx," 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 reinforced was that rofecoxib [Vioxx] had no cardiovascular toxicity: rather, naproxen was cardioprotective.

But Merck did not stop there. The company also apparently launched an aggressive campaign of intimidation against any researcher who was calling the safety of Vioxx into question. Before Dr. Topol and his colleagues published their article in 2001 questioning the safety of Vioxx Merck officials flew to

incident, Dr. Fries quoted Mr. Sherwood as saying that Dr. Signh's lectures were "irresponsibly anti-Merck and specifically anti-Vioxx" and that if this continued "Dr. Signh would 'flame out' and there would be consequences for myself and Stanford." Dr. Fries complained of a "consistent pattern of intimidation of investigators of Merck" on Vioxx.

Dr. Lee Simon, a rheumatologist from Boston and consultant to Pfizer on its competitor Cox-2 drug Celebrex, also received a call from Mr. Sherman after Simon reported that Vioxx might be associated with a risk of high blood pressure and swelling. "The company was trying to suppress a discussion about this data" he told the *Wall Street Journal*.^{viii} M. Thomas Stillman, a professor at the University of Minnesota, received a similar call from Mr. Sherwood after reporting a possible link between high blood pressure and taking Vioxx. Said Dr. Stillman, the call "had a tone to me of 'You better be careful what you are saying.'"^{ix}

By far the most aggressive posture Merck took to try and silence its critics involved Dr. Joan-Ramon Laporte of the Catalan Institute of Pharmacology in Barcelona, Spain.

THE MOST AGGRESSIVE POSTURE MERCK TOOK TO TRY AND SILENCE ITS CRITICS INVOLVED DR. JOAN-RAMON LAPORTE OF THE CATALAN INSTITUTE OF PHARMACOLOGY IN BARCELONA, SPAIN. IN THE SUMMER OF 2002, DR. LAPORTE EDITED A PUBLICATION THAT REPEATED CRITICISMS OF MERCK'S HANDLING OF VIOXX THAT HAD BEEN PREVIOUSLY PUBLISHED IN THE BRITISH MEDICAL JOURNAL. MERCK DEMANDED THAT DR. LAPORTE PRINT A "RECTIFICATION" AND WHEN DR. LAPORTE REFUSED TO CORRECT ANYTHING IN THE ARTICLE, MERCK SUED HIM. IN JANUARY OF 2004 A JUDGE DISMISSED THE SUIT.

years). This translates to an actual risk of heart attack or stroke in 1 in every 70 patients treated with Vioxx for one year in routine populations. Dr. Ray also noted that 40 percent of the Vioxx users he found did indeed have a prior history of cardiovascular disease, meaning that this drug was being heavily used by the population most likely to suffer these fatal or debilitating side effects.

Merck did not sit idle in response to these studies. Indeed, rather than conducting the study that its own researchers, Bombardier and Reicin

Cleveland to try and talk them out of it.^{vi}

But Dr. Topol was not alone. As reported by the *Wall Street Journal*^{vii} Merck officials actually threatened a number of physicians who were asking the wrong questions. In October of 2000 Louis Sherwood, a Merck official, called Dr. James Fries, a Stanford University Medical School Professor, to complain about another Stanford Professor who had formerly been sponsored by Merck, Dr. Gurkirpal Signh. In a letter of complaint sent to Merck after the

In the summer of 2002, Dr. Laporte edited a publication that repeated criticisms of Merck's handling of Vioxx that had been previously published in the British medical journal, *The Lancet*. Merck demanded that Dr. Laporte print a "rectification" and when Dr. Laporte refused to correct anything in the article, Merck sued him. In January of 2004 a judge dismissed the suit saying that Dr. Laporte's article was factually correct and ordered Merck to pay court costs.

What Merck Scientists Really Believed

While Merck scientists were publishing and presenting their spin on the VIGOR results and disputing claims of others, the discussions inside Merck took on a far different tone. Internal Merck documents show a concern for adverse cardiovascular results from the very beginning. In a November 21, 1996, memo leaked to the *Wall Street Journal*, a proposed trial is discussed to compare the gastrointestinal effects of Vioxx as compared to the other non-specific NSAIDs. In order to perform the study, however, the group taking Vioxx would have to be prohibited from taking aspirin. In such a trial, the memo states "there is a substantial chance that significantly higher rates" of cardiovascular problems would be seen in the Vioxx group.^x In an e-mail written by a Merck official in 1997, a similar concern is raised. Briggs Morrison of Merck argued that unless the group that got the Vioxx also took aspirin, "you will get more thrombotic events [blood clots] and kill the drug".

Obviously, the Merck scientists recognized the "anti-aspirin" effect of the COX-2s and theorized that if they did not also give the patients aspirin to offset that effect, then there would be an increase in blood clot-related side effects. Of course, because Merck was championing Vioxx as the drug that would replace aspirin and other NSAIDs that harmed the gastrointestinal tract, this posed a dilemma.

While publicly publishing articles after the VIGOR trial explaining that the difference in cardiovascular risk was not attributable to Vioxx, Merck's research chief Dr. Scolnick sent an e-mail on March 9, 2000, with the subject line "VIGOR." In the e-mail Dr. Scolnick indicated that the cardiovascular events associated with Vioxx "are clearly there" He went on to state that "it is a shame but it is a low incidence and it is mechanism-based as we worried it was." This latter statement is a likely reference to the known or theorized prothrombic effect of COX2's. Dr. Scolnick went on to suggest that before the results were made public he wanted other data available so "it is clear to the world" that this prothrombic effect is present in all COX-2s, not just Vioxx. This e-mail was sent just two months prior to

Merck issuing its press release in May 22, 2001, entitled "Merck Reconfirms Favorable Cardio-vascular Safety of Vioxx"

By this point it is clear that the marketing people were having more sway with Merck executives than were the scientists. In May of 2000 the company's top executives met to consider a study to get to the bottom of the cardiovascular risk of Vioxx. The marketing executives balked. "At present, there is no compelling marketing need for such a study" a PowerPoint slide prepared for the meeting stated. "Data would not be available during the critical [marketing] period. The implied message is not favorable".^{xi}

In 2001 Dr. Beepak L. Bhatt, a cardiologist at the Cleveland Clinic, proposed a study of Vioxx in patients with severe chest pain. Merck declined stating that the patients proposed for the study did not reflect typical Vioxx users.^{xii} In actuality, at least based upon the Vanderbilt study, over 40 percent of Vioxx users were, in fact, patients with cardiovascular disease, so Dr. Bhatt's proposed study did reflect typical Vioxx users.^{xiii}

Meanwhile, back at the FDA...

The FDA had approved Vioxx based upon the data from the VIGOR study submitted to the agency in 1999. This is the same data that Dr. Topol and his colleagues evaluated in 2001 and found a clear-cut association between Vioxx and adverse cardiovascular events. However, it was not until February of 2001 that the FDA Arthritis Advisory Committee first met to discuss this concern about Vioxx, which had been known for two years. As Dr. Topol wrote: "It remains unclear why the FDA waited two years after its review and approval of rofecoxib [Vioxx] to conduct this meeting."^{xiv}

Yet, even then nothing happened and the FDA took no action.

Although the Merck-employed authors of the published version of the VIGOR study had concluded that VIOXX was not the cause of the increased heart attacks and strokes, they also conceded that this premise "needs further confirmation in a larger study."^{xv} Dr. Topol and his colleagues stated in 2001 that "it is mandatory to conduct a trial specifically assessing cardiovascular risk

and benefit of these agents". In spite of this seeming agreement from both sides of the medical debate that a study was needed, the FDA did nothing. This inaction is all the more amazing in light of the estimate by Dr. David Graham, the Associate Director for Science of the FDA Office of Drug Safety that Vioxx had been associated with more than 27,000 heart attacks or deaths linked to cardiac problems.^{xvi} In testimony before a Senate Committee in November, Dr. Graham raised this estimate to "over 55,000".

While the FDA was sitting on its hands, Merck was not idle. Instead of conducting a study such as Dr. Bhatt at Cleveland Clinic had proposed, Merck was spending more than \$100 million (many times what a valid study would cost) on a direct marketing campaign to consumers urging them to ask their doctors to prescribe Vioxx. Although the FDA knew about the potential dangers of Vioxx and the lack of a study to clarify the issue and the fact that established NSAIDs were just as effective for most people and available at a fraction of the cost, the FDA did not stop Merck's direct-to-consumer campaign, something it has the regulatory authority to do. As a result, more than 10 million prescriptions per month were being written for Vioxx. The FDA did issue a warning letter to Merck in September of 2001 stating that Merck's promotional campaign for Vioxx "minimizes the potentially serious cardiovascular findings" of VIGOR. It required that Merck send a warning letter to doctors but did not slow Merck's direct marketing to the public of the virtues of Vioxx.

The Final Straws

In a trial of 2,600 patients that was designed to show a favorable effect for Vioxx on the incidence of colon polyps (the unpublished APPROVe study), it was revealed that the patients taking Vioxx had a 3.5 percent incidence of heart attacks and strokes compared to 1.9 percent for those taking a placebo. Since Merck could not argue that the placebo was cardio protective as it had with naproxen, Vioxx was withdrawn from the market.

The results of this trial compared favorably with the results of the Kaiser Permanente study which were made public in a memo dated

WHAT IS IRONIC IS THAT MOST PEOPLE WHO TOOK VIOXX WOULD HAVE RECEIVED THE SAME PAIN RELIEF FROM ONE OF THE OLD NSAIDS WITHOUT SUFFERING THESE RISKS.

Sept. 30, 2004,^{vii} (coincidentally the very day Vioxx was withdrawn from the market by Merck). In the memo written by Dr. Graham of the FDA to his superior, Paul Seligman, MD, the Acting Director of Drug Safety, Dr. Graham concluded from the Kaiser Permanente data that Vioxx increased the risk of serious coronary heart disease defined as acute myocardial infarction and sudden cardiac death by 3.7 fold for high dose (50mg/day) and 1.5 fold for standard dose (25mg/day) compared to celecoxib (Celebrex) use. Dr. Graham contends that his superiors at the FDA delayed his efforts to publish this study. One e-mail called his findings "nothing more than scientific rumor". Dr. Graham's study also concluded that naproxen had no cardioprotective effect, as Merck had been advocating since the VIGOR study came out. Graham concluded that based on his data naproxen may actually confer an increase in risk for these effects.

In the November issue of the British medical journal *The Lancet*^{viii}, a review and meta-analysis of all available data from trials of Vioxx was done. These researchers concluded as follows: "Our cumulative meta-analysis of randomized controlled trials indicates that an increased risk of myocardial infarction was evident from 2000 onwards. At the end of 2000, the effect was both substantial and unlikely to be a chance finding."

As Dr. Topol wrote in a commentary in the October issue of the *New England Journal of Medicine*, "considering the tens of millions of patients who were taking [Vioxx], we are dealing with an enormous public health issue...There may be tens of thousands of patients who have had major adverse events" due to this medication. Dr. Topol continued "...it is clear that Merck's commercial interest in [Vioxx] sales exceeded its concern about the

drug's cardiovascular toxicity". It is also clear that the FDA did nothing to provide a check on Merck's voracious appetite to rake in billions from this blockbuster drug.

Dr. Juni and his colleagues summed it up quite well in the conclusion to their *Lancet* publication in November of 2004:

If Merck's statement in their recent press release that "given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take" was appropriate in September, 2004, then the same statement could have and should have been made several years earlier, when the data summarized here first became available. Instead, Merck continued to market the safety of rofecoxib."

Conclusion

The Bush Administration seeks to grant immunity to companies like Merck whose drugs were approved by the FDA, even where, as here, the deaths and injuries occurred long after the company and the FDA knew or should have known that there were risks. What is ironic is that most people who took Vioxx would have received the same pain relief from one of the old NSAIDs without suffering these risks. Merck recognized that the group that was at risk for gastrointestinal bleeds from the older NSAIDs was too small to turn Vioxx into the blockbuster it became with 80 million people taking the drug in 2003 and total sales of \$2.5 billion dollars. That is why mass marketing to the general public was so crucial to the company's financial success. Moreover, Merck was a company that desperately needed a blockbuster. Several of its big earners were about to go off patent, meaning that they would soon be facing generic competition. Thus, the com-

pany made the affirmative choice to push Vioxx on the public through Madison Avenue rather than medicine.

As one doctor put it, discussing the cost/benefit ratio of taking Vioxx the established NSAIDs caused GI bleeding in 1 in 400 people, and GI bleeding is highly treatable. Vioxx caused cardiovascular effects in more than 1 in 100 patients who took it, and many of these were fatal. In other words, Vioxx (at a cost of approximately \$3 per pill compared to pennies per pill for other NSAIDs) was able to prevent one case of treatable GI bleeding for every 4 heart attacks it caused. Some bargain. And they say trial lawyers are to blame for the increasing cost of health care.

Fortunately for the public good, Merck will be forced to pay a price for its conduct in the form of thousands of jury awards and settlements to injured victims. This is the deterrent effect of products liability law, which imposes consequences on executives who choose profit over safety. However, if Merck and other drug makers are granted immunity due to product approval by an ineffective and highly politicized FDA, then what will prevent the Vioxx story from being repeated over and over again? Stay tuned. In the meantime, watch what you grab from the medicine cabinet for those aches and pains.

NOTES

i The unpublished Adenomatous Polyp Prevention on Vioxx (APPROVE) study.

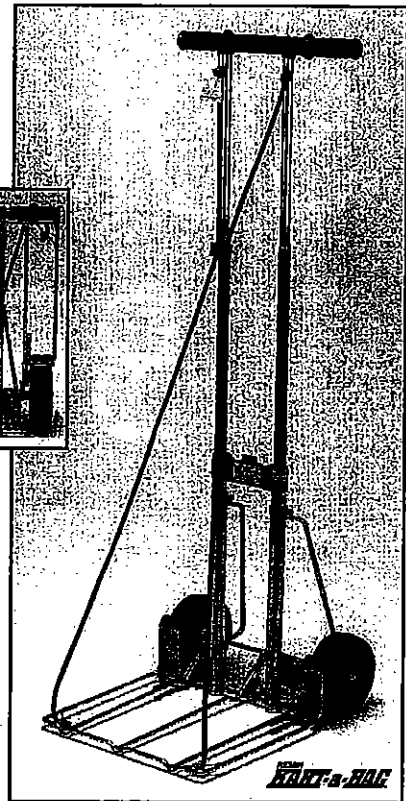
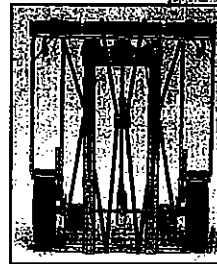
ii Bombardier C, Laine L, Reicin A, et al., Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343:1520-8.

iii Mukherjee DM, Nissen SE,

MOVE THOSE HEAVY BRIEFS WITH EASE

ON A ^{REMIN} **KART-a-BAG** SUPER 600.

- Carries 300 lbs.
- Easily retracts in to compact unit for storage.
- Made of high grade steel and aluminium.
- Shown with optional T-Bar handle
- Sturdy 6 inch rubber wheels.
- Overall dimensions:
Height: 48"; Base: 15.75" x 12.5"
- Storage dimensions:
Height: 20.25"; Width: 16"; Depth: 7"
- Storage weight: 13 lbs.
- Optional flight case available.
- Limited 10 year warranty.
- Made in USA since 1967



Order online or by phone.

www.kart-a-bag.com

800-423-9328 weekdays from 9-4 C.S.T.

510 Manhattan Road Joliet IL 60433

Outside US 815-723-1940 815-723-2495 f

Topol, EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954-9.

iv Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002; 360: 1071-1073.

v Topol, EJ, Failing the Public Health - Rofecoxib, Merck and the FDA, N Engl J Med 2004, 351:17 vi New York Times, Alex Berenson, et al., "Dangerous Data" November 14, 2004.

vii Wall Street Journal, Anna Wilde Mathews and Barbara Martinez, "Painful Drug", November 1, 2004.

viii Id.

ix Id.

x Wall Street Journal, Anna Wilde Mathews and Barbara Martinez, "Painful Drug", November 1, 2004.

xi Quoting New York Times Article, Alex Berenson, et al., "Dangerous Data" November 14, 2004.

xii Id.

xiii Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002; 360: 1071-1073.

xiv Topol, EJ, Failing the Public Health - Rofecoxib, Merck and the FDA, N Engl J Med 2004, 351:17

xv 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.

xvi New York Times, Alex Berenson, et al., "Dangerous Data" November 14, 2004.

xvii "Risk of acute myocardial infarction and sudden cardiac death in patients treated with COX-2 selective and non-selective, traditional NSAIDs, Memorandum, Department of Human Services, Public Health Service, Food and Drug Administration, Center for Drug Evaluation and Research, September 30, 2004.

xviii Juni P, Nartey L, Reichenbach S, Sterchi R, Dieppe P, Egger M, Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. ■