Vioxx: The Downfall of a Drug

Merck Tries to Move Beyond Vioxx Debacle

November 12, 2007 · 6:00 AM ET
Heard on Morning Edition

RICHARD KNOX

Listen

Merck agrees to pay nearly $5 billion to settle lawsuits from consumers contending the painkiller Vioxx caused heart attacks and strokes. The safety problems of Vioxx and the withdrawal of Vioxx from the market was a watershed event in regulating prescription drugs in the U.S.

LINDA WERTHEIMER, host:

Merck and Company has agreed to settle tens of thousands of lawsuits involving its blockbuster drug Vioxx for $4.9 billion. Merck does not acknowledge that Vioxx caused individual heart attacks.

NPR's Richard Knox reports the impact of Vioxx will be lasting.

RICHARD KNOX: Before Merck pulled Vioxx off the market three years ago, Americans could hardly avoid the Vioxx message.

(Soundbite of commercial)

Unidentified Man: Vioxx is here, a prescription medicine for the most common type of arthritis pain.

KNOX: Merck spent more to promote Vioxx than any drug company had ever spent before. And therein lies the first lesson of the Vioxx debacle, says Doctor Catherine DeAngelis. She's editor-in-chief of the Journal of the American Medical Association.

Dr. CATHERINE DeANGELIS (Journal of the American Medical Association): What people should learn from this is you don't believe anything, not one thing, put out by a pharmaceutical company. Just don't believe it. You start from there.

KNOX: DeAngelis says Vioxx represents the height of a drug industry trend that dates back 10 or 15 years, the ascendancy of marketing over science. Because of Merck's massive marketing push, most of the people who took Vioxx didn't need it.

Dr. DeANGELIS: Probably five to 10 percent of the people who took it really should have been taking it, because Vioxx for them worked. No other drug worked for them.

KNOX: She says for the other 90 percent, the drug raised the risk of a heart attack or stroke with no significant benefit.

Dr. DeANGELIS: When you want to make money by selling products to people who don't need it rather than putting your money into developing new drugs, then you're going to get into this kind of trouble.

KNOX: In Merck's push to turn Vioxx into a blockbuster, critics say the company ignored early signs that the drug greatly increased the risk of heart attacks.

Dr. Steven Nissen of the Cleveland Clinic says the episode is a powerful illustration of the dangers in the way new drugs get approved and quickly get widely used.

Dr. STEVEN NISSEN (Chairman, Cardiovascular Medicine, Cleveland Clinic): When new drugs are approved, there are often unresolved safety questions. The number of patients studied in the trials leading to drug approval can only be two, three, four thousand patients sometimes. And that's not enough to clearly see the risks associated with drugs.

KNOX: The Food and Drug Administration is supposed to monitor problems that crop up after a drug goes on the market. But Nissen says Vioxx shows how reluctant the FDA has been to force companies to do these so-called post-marketing studies.

Dr. NISSEN: In its recent report to Congress, the FDA acknowledged that only 14 percent of those post-marketing trials were ever conducted as intended.

KNOX: On September 27th, President Bush signed a new law that gives the FDA authority to fine companies that don't do these safety studies.

Dr. BRUCE PSATY (University of Washington): We'll see, if they get used. It won't be for the lack of the authority.

KNOX: That's Dr. Bruce Psaty of the University of Washington. He says it won't take long to see if the FDA uses its new authority.

Dr. PSATY: I expect new drugs to come on the market and have adverse effects. That necessarily mean it's a problem. The question is how rapidly was it identified?

KNOX: Catherine DeAngelis, the AMA journal's editor, agrees Vioxx is not the last of the nasty surprises.

Dr. DeANGELIS: This one they got caught, and I think we just have to be very vigilant about this.

KNOX: DeAngelis says she used to be skeptical of drug companies; now she's cynical. That may be the real legacy of Vioxx.

Richard Knox, NPR News.

WERTHEIMER: You can trace the rise and fall of Vioxx at npr.org.

Timeline: The Rise and Fall of Vioxx

November 10, 2007 · 2:40 PM ET

SNIGDHA PRAKASH

VIKKI VALENTINE


Vioxx® 12.5 mg
Vioxx® 25 mg

Merck voluntarily withdrew Vioxx from the market in 2004. Research published in the medical journal *Lancet* estimates that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died.

Brendan McDermid/EPA/Corbis

Shortly before the FDA approved Vioxx in 1999, drug maker Merck launched a study it hoped would prove that Vioxx was superior to older painkillers, because it caused fewer gastrointestinal problems. Instead, the study would eventually show Vioxx could be deadly, causing heart attacks and strokes.

Five years after Vioxx's launch, Merck withdrew the drug from the market. By that time, Merck had sold billions of dollars of the drug worldwide. A timeline of Vioxx's rise and fall:

November 1998: Merck asks the Food and Drug Administration (FDA) for approval of Vioxx, having tested the drug on 5,400 subjects in eight studies.

January 1999: Merck launches the Vioxx Gastrointestinal Outcomes Research study (VIGOR). With more than 8,000 participants, it is the largest study ever done of the drug. Half take Vioxx and the other half take naproxen. The clinical trial is designed to see whether Vioxx is safer for the digestive system than naproxen, an older painkiller.

May 1999: The FDA approves Vioxx, making the drug available by prescription in the United States.

October 1999: First meeting of the VIGOR study's data and safety monitoring board (DSMB). Study results as of Oct. 1, 1999, show that Vioxx patients have fewer ulcers

and less gastrointestinal bleeding than patients taking naproxen. It looks as if the study will be a success for Merck.

November 1999: At the second meeting of the VIGOR safety panel, the discussion focuses on heart problems. As of Nov. 1, 1999, 79 patients out of 4,000 taking Vioxx have had serious heart problems or have died, compared with 41 patients taking naproxen. The minutes of the panel's November meeting note that "while the trends are disconcerting, the numbers of events are small." The panel votes to continue the study and to meet again in a month.

December 1999: The safety panel holds its last meeting. It's told that as of Dec. 1, 1999, the risk of serious heart problems and death among Vioxx patients is twice as high as in the naproxen group.

The DSMB votes to continue study, but decides Merck needs to develop a plan to analyze the study's cardiovascular results before the study ends. DSMB Chairman Michael Weinblatt and Merck statistician Deborah Shapiro draft a letter and send it to Merck's Alise Reicin (now vice president of Merck's clinical research).

Later, when defending its decision to continue the study, the safety panel said it couldn't tell if Vioxx was causing the heart problems or if naproxen, acting like low-dose aspirin, protected people from them, making Vioxx just look risky by comparison.

January 2000: Merck balks at developing the analysis plan. The company wants to wait and combine the cardiovascular results of VIGOR with results from other Vioxx studies. Weinblatt, the safety panel chair and a rheumatologist with Brigham & Women's Hospital in Boston, pushes for immediate analysis.

February 2000: After further discussions, Merck and Weinblatt agree to analyze heart problems reported by Feb. 10, 2000 — at least a month before the last patient leaves the study. Events reported later won't be included in the initial analysis.

Feb. 7, 2000: Weinblatt fills out a financial disclosure form that says he and his wife own $72,975 of Merck stock.

Feb. 15, 2000: Weinblatt agrees to a new consulting contract with Merck. "We are delighted that you have agreed to serve as a member of the VIOXX Multidisciplinary Advisory Board," Merck writes in an invitation to Weinblatt to attend his first advisory board meeting.

Weinblatt signs the new contract on March 6. It involves 12 days of work over two years, at the rate of $5,000 per day.

March 2000: Merck gets results of the VIGOR trial.

May 2000: Merck submits VIGOR paper to the *New England Journal of Medicine* (NEJM) for publication. The data include only 17 of the 20 heart attacks Vioxx patients have.

July 5, 2000: A memo from Merck statistician Deborah Shapiro to Merck scientist Alise Reicin (both are listed as authors of the *NEJM* paper) refers to heart attacks 18, 19 and 20 suffered by patients taking Vioxx during the study.

July 2000/November 2000: VIGOR authors submit two sets of corrections to their *NEJM* manuscript. No mention of the three additional heart attacks.

Oct. 13, 2000: Merck tells the FDA about heart attacks 18, 19 and 20.

Nov. 23, 2000: The VIGOR results are published in *NEJM*, still with no mention of the three additional heart attacks in the Vioxx group. The published results also leave out data on many other kinds of cardiovascular adverse events.

February 2001: The FDA holds an advisory meeting on the VIGOR trials. It publishes complete VIGOR data on its Web site, including the additional heart attacks and data on other cardiovascular events.

Aug. 22, 2001: Cardiologists Debabrata Mukherjee, Steven Nissen and Eric Topol publish their meta-analysis in the *Journal of the American Medical Association*, based on complete VIGOR data that the FDA has made available.

Their analysis is significant because they take *all* the VIGOR data from the FDA Web site, recrunch them, and cast serious doubt on the hypothesis that naproxen protects the heart.

January 2002 to August 2004: Numerous epidemiological studies point to Vioxx's increased risk of cardiovascular problems.

September 2004: Merck withdraws Vioxx after a colon-polyp prevention study, called APPROVe, shows that the drug raises the risk of heart attacks after 18 months. By the time Vioxx is withdrawn from market, an estimated 20 million Americans have taken the drug.

Research later published in the medical journal *Lancet* estimates that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died.

July 14, 2005: NEJM editor-in-chief Dr. Jeffrey Drazen tells NPR that the journal had been "hoodwinked" by Merck, and that the authors of the VIGOR paper should have told the journal about the additional data.

August 2005: A Texas state jury returns a verdict against Merck in the first Vioxx liability case to go to trial. Some 13,000 lawsuits have been filed against the company on behalf of 23,000 plaintiffs who allege the drug caused heart attacks and strokes.

November 2005: *NEJM* executive editor Dr. Gregory Curfman is deposed in connection with the Vioxx product-liability cases. At that time, he learns about the July 5, 2000, memo, which shows Merck VIGOR authors knew about heart attacks 18, 19 and 20 well before the paper was published in *NEJM*.

December 2005: NEJM issues an "Expression of Concern," writing that "inaccuracies and deletions" in the VIGOR manuscript Merck submitted to the journal "call into question the integrity of the data." The journal asks the study authors to submit a correction to the journal.

March 2006: VIGOR study authors respond to *NEJM's* Expression of Concern: "Our evaluation leads us to conclude that our original article followed appropriate clinical trial principles and does not require a correction." The three heart attacks in question, say the authors, occurred after the study's "prespecified cutoff date" for reporting cardiovascular problems.

Journal editors stand by their call for a correction, replying that the cut-off date appeared to be selected shortly before the trial ended, and was a month earlier than VIGOR's cutoff date for gastrointestinal problems. Such a trial design, according to *NEJM*, "skewed" results.

May 2006: Outside analysis of data sent to the FDA from the Vioxx APPROVe study show that the cardiovascular risks from Vioxx began shortly after patients started taking the drug. The data also indicate that the risks from Vioxx remain long after patients stop taking the drug.

Merck disagrees with the analysis and maintains that patients aren't at risk unless they had taken the drug for more than 18 months.

This point is worth billions for Merck. Many of those suing the company say they took Vioxx for less than 18 months.

June 2006: The seventh trial against Merck begins, with plaintiff Elaine Doherty, 68, alleging the painkiller caused her heart attack and subsequent double heart bypass surgery. The trial, before the New Jersey superior court, is the first since the release of the new Vioxx research results. The data raises questions about how quickly the drug could cause harm and could undermine Merck's credibility.

Out of the six cases that have already gone to trial, Merck has won three and lost three.

Research published in the medical journal *Lancet* estimates that 88,000 Americans had heart attacks from taking Vioxx, and 38,000 of them died.

November 2007: Merck announces it will pay $4.85 billion to end thousands of lawsuits over its painkiller Vioxx. The amount, to be paid into a so-called settlement fund, is believed to be the largest drug settlement ever.

The Whitehouse Station, N.J.-based drug maker emphasized that it is not admitting fault.

The settlement lets Merck avoid the personal-injury lawsuits of some 47,000 plaintiffs, and about 265 potential class-action cases filed by people or family members who claimed the drug proved fatal or injured its users.

Related NPR Stories

Conflicted Safety Panel Let Vioxx Study Continue June 8, 2006

Q&A: Vioxx's Health Risks May 18, 2006

Q&A: Protecting Patient Safety In Drug Trials June 8, 2006

Related NPR Stories

Q&A: Post-Vioxx, Pain Relief Remains Complicated Nov. 9, 2007

Merck's Conditions for its $4.85B Settlement Fund Nov. 9, 2007

Merck to Ante Up $4.85B for Vioxx Settlements Nov. 9, 2007

More Stories From NPR

RESEARCH NEWS

Medical Journal Publishes Correction on Vioxx Study


ALL

HEALTH

Medical Journal Issues Vioxx Study Correction

RESEARCH NEWS

Study: Health Risk Remains a Year After Quitting Vioxx


morning
edition

LAW

Jury: Vioxx Maker Owes Heart-Attack Victim $9 Million

LAW

Merck Ordered to Pay $4.5 Million in N.J. Vioxx Case

RESEARCH NEWS

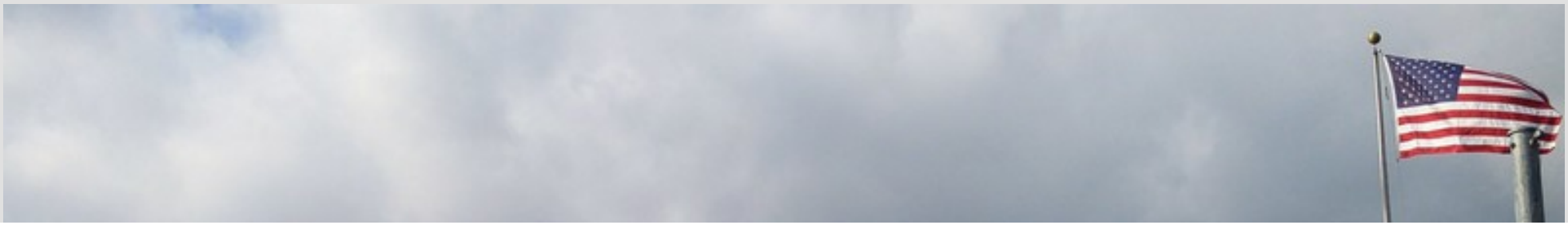
RESEARCH NEWS
Journal Raises New Questions About 2000 Vioxx Study

Popular on NPR.org

TECHNOLOGY
She Gets Calls And Texts Meant For Elon Musk. Some Are Pretty Weird

SCIENCE

Herd Of Fuzzy Green 'Glacier Mice' Baffles Scientists



NATIONAL

570 Workers Test Positive For Coronavirus At North Carolina Poultry Plant

NEW MUSIC

Carly Rae Jepsen Releases 'Dedicated Side B,' The Album We All Needed

NATIONAL

Georgia Authorities Arrest 3rd Man In Ahmaud Arbery Killing

HEALTH

Scientists Warn CDC Testing Data Could Create Misleading Picture Of Pandemic

NPR Editors' Picks

GLOBAL HEALTH

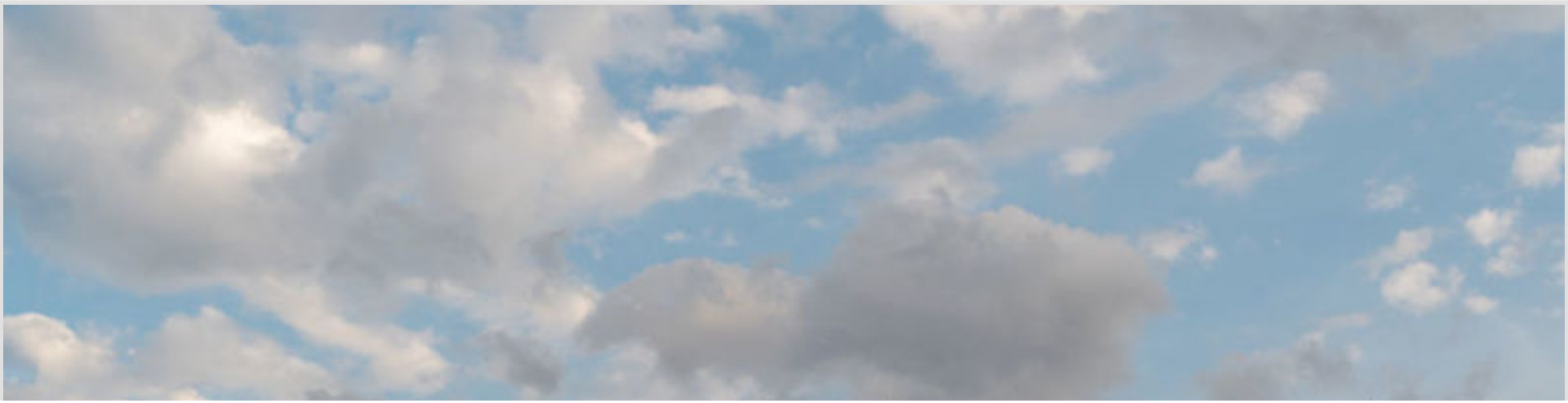
South Korean Study Shows No Evidence Recovered COVID Patients Can Infect Others

HEALTH

Food Banks Get The Love, But SNAP Does More To Fight Hunger

HEALTH

The Race For A Polio Vaccine Differed From The Quest To Prevent Coronavirus

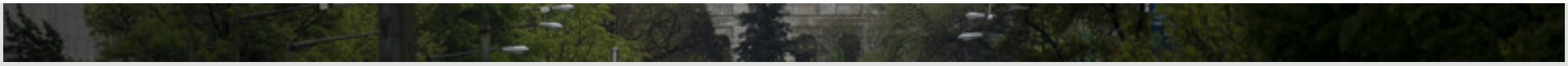


SHOTS - HEALTH NEWS

Scientists Say New, Lower CDC Estimates For Severity Of COVID-19 Are Optimistic

POLITICS

White House Looks At 'Opportunity Zone' Extension In Wake Of COVID-19



POLITICS

How The Coronavirus Has Affected Individual Members Of Congress

Vioxx: The Downfall of a Drug

privacy

your privacy choices

text only