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How the New England Journal Missed Warning Signs on Vioxx

Medical Weekly Waited Years To Report Flaws in Article That Praised Pain Drug

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BOSTON -- In August 2001, a Seattle pharmacist called a radio show on which Jeffrey Drazen, the top editor of the New England Journal of Medicine, was appearing. On the air, the pharmacist, Jennifer Hrachovec, begged Dr. Drazen to update an article in the journal that touted the benefits of the painkiller Vioxx while playing down its heart risks.

Dr. Hrachovec had been reviewing data on a Food and Drug Administration Web site indicating that patients in a Vioxx clinical trial had suffered more heart attacks than the journal article about the trial reported. "It bothers me there is more data from the trial than has ever been published and the New England Journal still hasn't published an editorial or any kind of update," she said. "My concern is that doctors are still using this and exposing their patients to higher risks of heart problems and they just don't even know that that's the case."

On Record

Pharmacist Jennifer Hrachovec challenged Jeffrey Drazen, editor of the New England Journal of Medicine, about the Vigor study in a call to a Seattle radio show Aug. 14, 2001. Below, excerpts.

Hrachovec: "With this study in particular, it bothers me that there is more data from the trial than has ever been published and the New England Journal still hasn't published an editorial or any kind of update to let readers and clinicians using this drug and giving it to patients who they think will benefit from a better side-effect profile. My concern is that doctors are still using this and exposing their patients to higher risks of heart problems and they just don't even know that that's the case."

Drazen: "… We can't be in the business of policing every bit of data that we put out. We think that that's the role of people who know the field. And when they think that the field has advanced to the point where something which was true at the time it came out may no longer be true … having brought that

Dr. Drazen was dismissive. "We can't be in the business of policing every bit of data we put out," he told Dr. Hrachovec.

Three years later, Merck & Co. pulled Vioxx from the market, citing higher risk of heart attacks and strokes in some patients. An estimated 20 million Americans took Vioxx, and more than 11,500 lawsuits have been filed against Merck alleging death and other damage from the drug.

While Merck has taken the brunt of criticism in the affair, the New England Journal's role in the Vioxx debacle has received little attention. The journal is the most-cited medical publication in the world, and its November 2000 article on Vioxx was a major marketing tool for Merck.

Last December, the journal repudiated the Vioxx article in an "expression of concern," but only after the drug had been

evidence to our attention in the form of a manuscript or a letter, we can judge whether there's enough new information and put it out if we believe that the re-analysis is correct."

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Listen to the full exchange on the Web site of KUOW, Puget Sound Public Radio. (Hrachovec's call begins at about minute 44:30.)

recalled and more than five years after the article appeared. Had the journal acted before the recall, its authoritative voice almost certainly would have damped the Vioxx boom.

Dr. Hrachovec's radio-show call was one of several early warnings about the article's flaws including its failure to mention the extra heart attacks. She and a colleague also submitted a letter to the New England Journal, which was rejected for publication. The Journal of the American Medical Association reported on Vioxx's cardiac risk in an August 2001 article. In April 2002 the FDA added a caution on Vioxx's label that warned of cardiovascular risks.

Internal emails show the New England Journal's expression of concern was timed to divert attention from a deposition in which Executive Editor Gregory Curfman made potentially damaging admissions about the journal's handling of the Vioxx study. In the deposition, part of the Vioxx litigation, Dr. Curfman acknowledged that lax editing might have helped the authors make misleading claims in the article. He said the journal sold more than 900,000 reprints of the article, bringing in at least $697,000 in revenue. Merck says it bought most of the reprints.

Stanford University medical professor Gurkirpal Singh, a rheumatologist who was among the first researchers to raise questions about Vioxx's cardiac risks, says the affair shows that journals need to be more vigilant about problems in what they publish. While praising the New England Journal for eventually taking action, he says "They absolutely should have corrected in 2001." Had it acted earlier, he says, sales of Vioxx "would have been killed."

Dr. Drazen, the editor, says in an interview that the authors of the article, who included Merck employees and consultants, are the ones at fault. "This was an episode where it was clear people had taken data and not reported it fully," he says in an interview. He adds: "I have now learned we need to be much more careful."

The questions about the New England Journal come as the flaws of leading medical journals are receiving greater attention. Many articles lend an academic imprimatur to messages hatched by drug companies as part of publicity campaigns. Sometimes they fail to disclose authors' financial ties to companies or the involvement of company-hired ghostwriters.

Started in 1812, the New England Journal has 200,000 subscribers and is considered must reading for doctors who want to stay current. Its selectivity and editing practices are feared and respected. The weekly rejected 93% of the 3,586 manuscripts it received last year. Accepted papers typically undergo months of editing, including "peer review" by a secret panel of experts and scrutiny by staff editors, many of whom are doctors.

The journal won't disclose its revenue, but its owner, the nonprofit Massachusetts Medical Society, listed $88 million in total publishing revenue for the year ending May 31, 2005.

In May 2000, a team including Merck employees submitted to the journal an article about Vioxx, a painkiller approved the previous year by the FDA. The article presented the results of a human trial called Vigor that showed Vioxx posed a lower risk of stomach ulcers and bleeding than naproxen, one of a class of older pain relievers long associated with such complications.

The article said 0.4% of the Vioxx patients had suffered heart attacks, compared to 0.1% for the naproxen group. It offered several reasons why that wasn't as worrisome as it seemed, including a theory that the difference stemmed from naproxen's supposed protective effect on the heart. The New England Journal published the article on Nov. 23, 2000, and the occasion was celebrated by Merck in a press release.

Merck submitted data from the Vigor study to the FDA because it wanted to add the favorable information about stomach side effects to Vioxx's label. But the data it gave to the agency, posted on the FDA's Web site in February 2001, did not square with the data in the New England Journal article. Merck said Vioxx takers had 20 heart attacks, which translated into 0.5% of the total, not 0.4% as the article said. The higher figure undermined an assertion in the article that only those who were already at high risk of a heart attack showed an increased risk after taking Vioxx. That's because the extra heart attacks were all in the low-risk group.

The FDA Web site said Merck submitted the revised heart-attack data in October 2000, before the publication of the article. Dr. Curfman, the journal's executive editor and a cardiologist, acknowledges that he reviewed the FDA Web site posting around September 2001. The journal says the editors believed the FDA had posted late data from the trial that had not been analyzed in time to be included in the article's manuscript.

In June 2001, Dr. Hrachovec in Seattle and a doctor reviewing the drug for a Seattle health insurer wrote to the New England Journal, noting the FDA posting. They warned the journal that the Vioxx results it printed were incomplete and made the drug appear safer than it was. The journal refused to publish the letter, saying space was limited. It acknowledges that during this period it never asked Merck, the FDA or the article's authors about the discrepancy, believing that it was the responsibility of the authors to report new data.

Merck says the extra heart attacks, three in total, happened after a predetermined cutoff date for recording events in the trial. Merck says the article was properly done and doesn't require a correction. That puts the company at odds both with critics of the New England Journal and the journal's editors, who now are calling for a correction while defending their failure to ask for one earlier.

Dr. Drazen says journal editors are "just the middleman in picking what goes out there" and "when there are problems the onus lies with" authors to sound the alert. "If you ask me, it is none of our concern about whether [Vioxx] is a cardiovascular risk in the patients that are on trial," he says. The concern was making sure what was published was correct, he says, and "people could have set the record straight."

Early Criticism

Besides the article's possible understating of the heart-attack numbers, its theory that naproxen had a protective effect on the heart also came in for early criticism. "This hypothesis is not supported by any prospective placebo-controlled trials with naproxen," an FDA official wrote in a memo also published on the agency's Web site in February 2001. In September of that year, the FDA sent a public warning letter to Merck, criticizing the drug maker for promoting the naproxen idea without explaining the lack of evidence for it.

Curt Furberg, a Wake Forest University public health professor, says the New England Journal should have challenged the authors on the naproxen theory during the article's editing. "Here we have an editorial board attacking the company when they conducted an inferior review of the article," says Dr. Furberg, who is also an adviser to the FDA on drug safety. "The sad thing is patients have suffered as a result."

In September 2004, Merck withdrew Vioxx, citing the results of a new study that showed the drug raised the risk of heart attack and stroke for those using it at least 18 months.

Both sides in federal litigation over Vioxx conducted a deposition in November 2005 of Dr. Curfman, the executive editor. Plaintiffs hoped to bolster their allegation that Merck's marketing of Vioxx was deceptive.

Although the New England Journal wasn't on trial for anything, the deposition produced a number of damaging admissions by Dr. Curfman. He acknowledged that neither the peer reviewers nor journal editors challenged the authors' heart-attack theory about naproxen as it was presented in the article. "Yeah, we signed off on this," he said, according to a transcript of his testimony. "And I have many times had second thoughts about having done that."

Dr. Curfman also disclosed that the journal sold 929,400 reprints of the article -- more than one for every doctor in the country. Merck says it bought most of them. The reprints brought in between $697,000 and $836,000, using per-copy price estimates provided by the journal. If the New England Journal had questioned the article's findings earlier, the impact of the reprints likely would have been blunted because any corrections or official statements on a study must be included with the reprint. Merck says that after February 2001 it included a letter with the reprints telling doctors about the additional information submitted to the FDA.

Further Reading

Read the "Expression of Concern" published by the New England Journal of Medicine Dec. 29, 2005, about the Vigor trial.

The journal's editors grew alarmed about the potential for bad publicity over the videotaped deposition, fearing it could be leaked or played in a federal courtroom session on Dec. 8, according to internal emails and an interview with Drs. Curfman and Drazen. After five years of silence on the article, the editors started racing to prepare an "expression of concern" about it.

The New England Journal says there was a good reason for the sudden decision to rebuke the article's authors. It says Dr. Curfman was surprised to discover from a July 5, 2000, memo he was shown during the deposition that two of the authors who worked for Merck knew of the extra three Vioxx heart attacks well in advance of the November article.

However, that shouldn't have been news to Dr. Curfman since he says he read the FDA documents in 2001 showing Merck submitted information about the three events to the FDA more than a month before the article's publication.

Dr. Curfman says there was nothing in the FDA data to indicate the authors knew of the additional heart attacks. Also, he says, "The data were in the hands of a regulatory agency and we felt it was now up to them to take appropriate action."

Dr. Drazen also received a clear description of the timing in a July 2005 email from Eric Topol, then a Cleveland Clinic cardiologist, who had criticized Merck and Vioxx. Dr. Topol, who had been contacted by a National Public Radio reporter asking about the November 2000 New England Journal article, told Dr. Drazen that the article's authors "clearly had ample time to correct the data when one compares the FDA Submission dates and the galley proofs (as relayed to me by Greg Curfman)."

On the night of Dec. 7, Edward W. Campion, a senior New England Journal editor, sent a note to his staff explaining why the statement had to be released the next day. The explanation didn't involve any late-breaking information obtained by Dr. Curfman. "The reason is that tomorrow's testimony in the Vioxx trial

may involve part of a deposition that Greg gave," Dr. Campion wrote. "It will be essential to notify press" about the statement "and make it prominent" on the journal's Web site, he added.

A public-relations specialist who has advised the journal since 2002 predicted the rebuke would divert attention to Merck and induce the media to ignore the New England Journal of Medicine's own role in aiding Vioxx sales.

"I believe that given what a public punching bag Merck has become, there is more than enough information and more than enough context in the statement to drive the media away from NEJM and toward the authors, Merck and plaintiff attorneys," wrote Edward Cafasso, a Boston-based public relations consultant, in a late-night email to journal staffers hours before the expression was released. Mr. Cafasso later added, "In my view, this disclosure may very well be seen as the final straw for Merck on the Vioxx matter."

Mr. Cafasso's prediction initially proved correct. The Texas court ended up delaying the release of Dr. Curfman's deposition, and the expression of concern released Dec. 8 received wide media attention.

A Dec. 12 list of talking points circulated among journal editors advised them to deny that the journal's statement was connected to the federal trial. If asked about the release date, editors were advised to say, "We made this information public as soon as we could, without regard to the trial." It isn't clear who wrote the memo.

The editors now concede the timing was connected to the planned release of Dr. Curfman's deposition at the trial. "We wanted a coherent statement to go out before that," says Dr. Curfman. However, they maintain that the statement was motivated by Dr. Curfman's discovery of new information about the Merck authors' advance knowledge of the three heart attacks.

'We Were Hoodwinked'

Dr. Drazen says one discovery he made after the journal's statement was published shows how the authors deceived the journal. He found that the Vigor study of Vioxx continued to tally stomach-related events for several weeks after it stopped tallying heart-related events. "We were hoodwinked," he says. Merck says these cutoff dates were determined ahead of time and weren't designed to reduce the number of heart events included in the totals.

Perhaps the most sensational allegation in the journal's expression of concern was that the authors of the November 2000 article deleted heart-related safety data from a draft just two days before submitting it to the journal for publication. The journal said it was able to detect this by examining a computer disk submitted with the manuscript.

The statement was ambiguous about what data the authors deleted, hinting that serious scientific misconduct was involved. "Taken together, these inaccuracies and deletions call into question the integrity of the data," the editors wrote.

In reality, the last-minute changes to the manuscript were less significant. One of the "deleted" items was a blank table that never had any data in it in article manuscripts. Also deleted was the number of heart attacks suffered by Vioxx users in the trial -- 17. However, in place of the number the authors inserted the percentage of patients who suffered heart attacks. Using that percentage (0.4%) and the total number of Vioxx users given in the article (4,047), any reader could roughly calculate the heart-attack number.

Dr. Curfman says it would have been easier on readers to give the exact number and admits "both the

authors and the editors slipped up" in not including it.

Many news organizations, including The Wall Street Journal, misunderstood the ambiguous language and incorrectly reported that the deleted data were the extra three heart attacks -- which, if true, would have reflected badly on Merck. The New England Journal says it didn't attempt to have these mistakes corrected. Dr. Curfman says the language about the deletions is "very precise and it is correct."

The day after the expression of concern, Mr. Cafasso emailed colleagues: "The story is playing out exceptionally well."

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