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A FAILURE TO ASK THE RIGHT QUESTION

In November 2000, the *New England Journal of Medicine* published the Merck-funded VIGOR trial, which compared Merck's Vioxx (rofecoxib) to generic naproxen, a typical non-steroidal anti-inflammatory painkiller sold over-the-counter as Aleve, in patients with rheumatoid arthritis. While the primary results showed the drugs were comparable for pain and the new COX-2 inhibitor caused fewer gastrointestinal side effects, the Vioxx users had more than twice as many cardiovascular problems and five times as many heart attacks. To minimize those risks, the study authors suggested that the increase in heart attacks may have been due to naproxen having heart protective attributes similar to low-dose aspirin.

Over the next several months, prominent cardiovascular researchers associated with the Cleveland Clinic revisited the data not just in the VIGOR trial but in three other trials involving Pfizer's COX-2 inhibitor Celebrex (celecoxib). In August 2001, they published a Special Communication in the *Journal of the American Medical Association* warning about the risk of cardiovascular events with the new class of drugs. They called for further trials to "characterize and determine the magnitude of the risk."

This week, a Food and Drug Administration Advisory Committee is holding a three-day hearing to evaluate the magnitude of that risk. They will be presented with meta-analyses of existing trials; post-hoc epidemiology studies of large populations that took the drug; and re-analyses of data in trials whose primary outcomes had nothing to do with measuring heart disease. What they won't see is a well designed, placebo-controlled clinical trial that asked what the Cleveland Clinic researchers in August 2001 said should be asked.

The Center for Science in the Public Interest conducted a systematic review of the studies that have appeared in the academic literature since the JAMA article questioned the safety of COX-2 inhibitors. CSPI looked at all published trials for Vioxx, Celebrex and Bextra. The study found that no researchers funded by either the public or private sector published a study specifically designed to measure the risk of heart attacks or strokes from COX-2s.

"The failure of researchers in both the private and public sectors to follow up on the critical safety questions raised in one of the earliest large trials for these drugs points out the need for an independent safety arm at the Food and Drug Administration to require such trials and independent researchers to conduct them," said Merrill Goozner, director of the Integrity in Science project at the Center for Science in the Public Interest. "Industry managed to enroll tens of thousands of patients in clinical trials aimed at selling more of these drugs, but none in a trial designed to measure the risk of heart attacks or strokes."

The findings:

Since August 2001, the three approved COX-2 inhibitors have been tested in at least 237 clinical trials involving over 75,000 patients. The funding source was not disclosed or could not be determined for 93 of those trials. But in 103 of those trials, the companies behind the drugs – Merck and Pfizer – either funded the trial itself or provided financial support to the researchers. The other 41 trials were funded either by government or non-profit institutions.

Just 16 (15.5 percent) of the industry-funded trials evaluated any type of health risk associated with the drugs and only five (4.9 percent) of those had anything to do with cardiovascular risk. Four of those five (one by Merck and three by Pfizer) were very short term and designed to measure narrow questions like drug-drug interactions among patients with other cardiovascular problems. One Merck-funded French study of nearly 3,000 patients over 24 weeks suggested Vioxx did not cause an excess of thrombotic events, but the authors warned “this should be confirmed by large controlled clinical trials with a longer follow-up.”

Among the trials whose funding could not be determined, four trials dealt with cardiovascular risk. There was one reanalysis of data in the original trial used to gain FDA approval for Celebrex. The reanalysis claimed the drug did not cause cardiovascular side effects. But it’s important to note that the original study was not designed to detect such risk. The three other trials were short-term trials looking at specific issues like drug-drug interactions and not long-term trials designed to measure the overall cardiovascular impact of taking COX-2 inhibitors.

Public and non-profit institutions were no better at putting safety and heart health at the top of their agendas. Of the 41 trials not funded by industry, just eight (19.5 percent) asked questions related to potential side effects of COX-2 inhibitors and none of those involved cardiovascular risk.

So if it didn’t ask the big question, what did industry use its research-and-development budgets to study? The vast majority of the industry-funded trials in the literature were “seeding” trials: clinical trials for common but off-label uses of drugs that have already been approved for narrower indications. The idea is to get results published in a wide range of journals so that salespersons can deliver reprints to physicians in those specialties. Nearly 85 percent (87 of 103) of industry-funded trials that have appeared in the academic literature since 2001 involved testing the pain relief afforded by COX-2 inhibitors for off-label uses. A typical example: Merck funded 12 physicians associated with the Altoona Center for Clinical Research to test Vioxx against a traditional non-steroidal anti-inflammatory drug made by one of its rivals for arthritis of the knee. The results, published last year in the *Journal of the American Geriatric Society*, showed both worked, both were well tolerated and Vioxx offered slightly faster pain relief.

It is interesting to note that among the 93 trials whose funding was undisclosed or could not be determined, seeding trials accounted for nearly 90 percent of the total (83 of 93). This suggests that a high proportion of the trials whose funding couldn’t be determined were also industry-funded.