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Rx Needed for Medical Journals

Drug companies influence research; they also affect what gets published.

By Sonia Shah *January 10, 2002*

Why did the esteemed Journal of the American Medical Association publish a paper showing that blockbuster anti-arthritis drug Celebrex is superior to a $7 bottle of ibuprofen, while the FDA maintains it isn't? Because the scientists who wrote the paper–their expenses paid by Celebrex manufacturer Pharmacia–selectively omitted half their study data to make the boss's drug look good.

The Celebrex case isn't an aberration, according to Public Citizen's Dr. Sidney Wolfe. "People are injured and killed as a result of incomplete data being published and studies being designed in the wrong ways," he says. Corporate researchers attempt to prove marketing claims, not insure public health, critics say, so results are buffed or buried even if it means impeding doctors' understanding of illness and health.

The problems, however, go beyond eager-to-please scientists and eager-to-earn corporations. Medical journals are themselves reliant on drug-industry largesse. As a result, they are ill equipped to exclude unsavory, publicity-seeking corporate research from their public platform.

In September, in an unprecedented joint editorial, editors of thirteen leading medical journals, including *JAMA* as well as *The New England Journal of Medicine*, *The Lancet* and *The Annals of Internal Medicine*, announced a plan to fight back. Along with previously required disclosures about funding, conflicts of interest and scientific contributions, they declared they would also require authors to confirm that their sponsors gave them independent access to data and control over their publication. (Even the standard disclosures required by hundreds of journals have had limited success. Tufts University's Sheldon Krimsky analyzed the 1997 editions of more than 200 journals, finding that more than half hadn't published a single disclosure, a percentage that is startling given widespread industry support and participation in biomedical research.)

"The pharmaceutical industry has academic clinical investigators in a corner," explains Richard Horton, editor of *The Lancet*. Medical research on human subjects is poorly funded by the federal National Institutes of Health, Horton and others contend, because the agency favors the control and precision of laboratory science in which experimental subjects don't have complicated needs and rights. The result, not surprisingly, is that academic researchers often turn to the drug industry for cash. Corporations now fund 70 percent of all clinical research conducted in this country. Most of this research is "careful, good work," says former editor of *The Annals of Internal Medicine* Frank Davidoff. Even so, company sponsors see the academic work they fund as "marketing primarily, not scientific research," he says.

The problems start when expensive, time-consuming clinical trials paid for by the corporations produce negative results that contradict marketing claims. "The academics want to be able to take that information and tease it apart, to look at the good parts and the bad parts too. But the pharmaceutical companies' marketing departments are going to say they don't want to report on the bad stuff," says Dennis DeRosia, chair-elect of the Association of Clinical Research Professionals. In extreme situations, the struggle for control over data resorts to mudslinging and lawsuits. The Immune Response Corporation, for example, slapped a $10 million lawsuit on scientists it had hired to study its therapeutic vaccine Remune who wanted to publish results showing that Remune was ineffective. "I spent over $30 million," the company's president complained to the *Baltimore Sun*. "I would think I have certain rights." The case was eventually settled out of court, and the study was published in the November 1, 2000, *JAMA*.

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In such cases, journals' new rules may help scientists negotiate better contracts with their industry sponsors. But there is no antidote to the problem of subtle, pro-industry bias toward positive results when scientists are more than willing to sign on. A case in point is the controversy over the recent study of Celebrex, funded by Pharmacia and Pfizer. "Super-aspirins" such as Celebrex and Merck's Vioxx were developed to improve upon cheaper, over-the-counter remedies like ibuprofen by reducing the incidence of bleeding ulcers and other gastrointestinal side effects. With just a year of aggressive marketing to consumers (later condemned by the FDA as misleading), Celebrex sales leapt to $1.3 billion, even though FDA-required warning labels on the product stated that its advantage over ibuprofen–which costs about a third of what Celebrex does–was essentially unproven.

In September 1998 Pharmacia and Pfizer launched a study of more than 8,000 patients, overseen by industry scientists and hired academics from eight major universities, seeking to prove to the FDA that Celebrex deserved freedom from the stigmatizing warning labels affixed to competitors ibuprofen and diclofenac. The findings of the study were uninspiring. Celebrex patients developed ulcer complications more than twice as often as researchers expected, and this rate was statistically indistinguishable from the rate for patients taking the comparison drugs. But the study was a huge one, with thousands of patients and reams of data–surely some other conclusion could be made. And indeed, upon closer inspection, the researchers found that they could demonstrate a slight, qualified advantage for Celebrex if they left out the second six months of the study. A statistical anomaly–the faster dropout rate of susceptible patients in the comparison group–could shore up such a step.

While this move may have made Celebrex look marginally better than its competitors, it also diminished the study's clinical significance. "People aren't on these medications for six months; most are taking them for years on end," says Dr. David Lichtenstein, a gastroenterologist at the Boston University School of Medicine. But what's worse, critics say, is that the team's September 13, 2000, *JAMA* paper on the study neglected to mention that portions of the data had been selectively omitted.

Those academics "had full control over the data and publication" of the study, Pharmacia's vice president of medical affairs, Dr. John Fort, assured me. Perhaps so. But they also have industry ties even beyond those they disclosed publicly. What *JAMA* readers did not hear about is that one academic author is an epidemiologist mired in controversy over his claims that the doomed diet drug Redux was safe and effective while he was on the manufacturer's payroll, another is a rheumatologist whose smiling face appears prominently on the Celebrex website, and a third is a partner in a venture capital firm.

A casting glitch raised the curtain on Pharmacia's behind-the-scenes data manipulation. Upon request by JAMA editors, Lichtenstein and gastroenterologist Dr. M. Michael Wolfe reviewed Pharmacia's paper and wrote a tepidly favorable editorial to accompany it. But six months later, Wolfe sat on the FDA committee that considered the study in its entirety–a vantage point from which Celebrex's apparent advantage disappeared. He told the Washington Post he was "furious ... I looked like a fool." The FDA rejected the label-change application. But the JAMA paper had already gone public, and by confirming the marketing hype, "probably ha[d] more impact than our labeling," an FDA official told the Post.

Sometimes the unseen data are more alarming than the seen. Perhaps the most famous case dates back to 1978, when *The New England Journal of Medicine* reported that Ciba-Geigy's gout drug Anturane had been found to reduce the incidence of fatal heart attacks in people who had suffered at least one previous heart attack. The finding was hailed by the *New York Times* as one of the most important medical advances of the decade–until the FDA alerted journal editors that they were rejecting the new use for the drug. While it did indeed reduce the incidence of cardiac deaths, it increased deaths overall.

Journal editors wring their hands over such debacles, but the reality is that medical journals must curry favor with drug-company marketing execs. "If we publish a study that finds positive results, then the industry is delighted and buys lots of reprints," *Lancet* editor Horton confirms. According to insiders, *The Lancet*'s parent company, Reed Elsevier, contractually requires Horton to increase the journal's revenues by 10 percent a year. Given flat subscription rates, that means increasing reprint revenues, which now exceed the journal's subscription income, says Davidoff, the former *Annals of Internal Medicine* editor.

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Most medical journal editors don't muddy their hands with advertising decisions, but the companies and societies that pay their salaries are not above agitating for a bigger piece of the $5 billion drug-industry advertising pie–and forcing editors to make their pages as industry-friendly as possible. Reed Elsevier's Excerpta Medica helps companies place positive articles about their drugs in top-tier medical journals, many of which are conveniently owned by Reed Elsevier. Last spring the American Medical Association and the Massachusetts Medical Society, publishers of *JAMA* and *The New England Journal of Medicine*, respectively, funded a study with little clinical application: It showed that ads in their journals' pages more effectively boosted drug sales than expensive television spots aimed at consumers.

The Massachusetts Medical Society, which earns more than three-quarters of its income from journal revenues, pushes editors to be even more amenable to industry dollars, critics say. In a controversial 2000 move, for instance, the society replaced its independent-minded editors with asthma specialist Dr. Jeffrey Drazen, who had ties to more than twenty companies (which he said he would sever before assuming his new post). Drazen's effusive praise for Sepracor's drug levalbuterol, which he was paid to evaluate, was featured in company advertising materials and was later criticized as overstated by the FDA.

Given all this, the journals' new rules are certainly a step in the right direction. But publishing rules alone won't dam the tidal wave of industry dollars sweeping through medical research and publishing, with the very real risk of bias those dollars represent. Ultimately, clinical research must be supported with greater independent funding, and there should be federal rules that ban corporate participation in research the pharmaceutical industry does sponsor. Until then, public health is likely to continue to take second place to private gain.