Risk of death from rofecoxib in some trials may have been misrepresented by study sponsor

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A comparison of internal company documents, data submitted by the company to the FDA, and published clinical trial results indicates that the risk-benefit profile of rofecoxib in clinical trials involving patients with cognitive impairment may have been misrepresented by study sponsor Merck, according to an article in the April 16 issue of JAMA.

“Sponsors have a marketing interest to represent their products in the best light. This approach conflicts with scientific standards that require the symmetric and comparable reporting of safety and efficacy data. Selective reporting of the results of clinical trials can misrepresent the risk-benefit profile of drugs,” the authors write.

Bruce M. Psaty, M.D., Ph.D., and Richard A. Kronmal, Ph.D., of the University of Washington, Seattle, conducted a review of documents to summarize how the study sponsor represented findings regarding the risk of death associated with rofecoxib in clinical trials of patients with Alzheimer disease or cognitive impairment. The documents became available during litigation related to rofecoxib involving Merck, including internal company analyses and information provided by the sponsor to the Food and Drug Administration (FDA). The authors also evaluated information in two published articles that reported results of these trials.

In one article (reporting results of protocol 091) published in 2004, 11

"non-drug related deaths" were reported (9 deaths among 346 rofecoxib patients and 2 deaths among 346 placebo patients). In another article (reporting results of protocol 078) published in 2005, 39 deaths were reported among patients taking study treatment or within 14 days of the last dose (24 among 725 rofecoxib patients and 15 among 732 placebo patients) and an additional 22 deaths in the off-drug period (17 in rofecoxib patients and 5 in placebo patients). "However, these articles did not include analyses or statistical tests of the mortality data, and the two articles concluded that regarding safety, rofecoxib is 'well tolerated,'" the authors write.

In contrast, in April 2001, the company's internal intention-to-treat analyses (data analysis technique based on evaluation of patients in the study group to which they were randomly assigned) of pooled data from these two trials identified a significant three-fold increase in total mortality, with overall mortality of 34 deaths among 1,069 rofecoxib patients and 12 deaths among 1,078 placebo patients. "These mortality analyses were neither provided to the FDA nor made public in a timely fashion," the authors write. The data submitted by the sponsor to the FDA in a Safety Update Report in July 2001 used on-treatment analysis (a data analysis technique based only on evaluation of patients who were actually taking the drug or placebo they were assigned to take) methods and reported 29 deaths (2.7 percent) among 1,067 rofecoxib patients and 17 deaths (1.6 percent) among 1,075 placebo patients. "This on-treatment approach to reporting minimized the appearance of any mortality risk," they add. Deaths that had occurred more than 14 days after discontinuation of the trial drug apparently were not included.

In December 2001, when the FDA raised safety questions about the submitted safety data, the sponsor did not bring these issues to an institutional review board for review and revealed that there was no data and safety monitoring board (DSMB) for the protocol 078 study.

During additional follow-up time for the 078 study, there were approximately 8 excess deaths among those randomly assigned to receive rofecoxib, which was also associated with an increased risk of progression to Alzheimer disease, “a finding that was apparent early in the trial. The mortality findings and the Alzheimer disease findings would, in our judgment, have prompted a DSMB, if it had existed, to stop the trial early,” the researchers write.

“The only human-subjects protections available to the study participants were those provided by the investigators who were blind not only to the treatment allocation but also to the findings for study-wide adverse events, and by the unblinded Merck investigators, who did not discern a safety issue. The sponsor’s submission of individual adverse event reports over time to the FDA is not adequate for active trial monitoring. The FDA depends on the sponsor and the DSMB to alert the agency about any evidence of harm that may be associated with the drug.” They add that all large clinical trials, especially for drugs with known serious risks, should have a DSMB.

“Sponsors have a direct financial interest in their products and a fiduciary duty to shareholders to provide a return on their investment. These interests disqualify sponsors from other important duties, including those normally accorded to DSMBs and institutional review boards (IRBs). Failure of the sponsor to inform IRBs of a safety issue violates the trust of those human participants who volunteered to advance science, medicine, and public health.”

“For sponsors that conduct their own studies or use contract research organizations to conduct studies, it is not clear how transparency in the reporting of results can be achieved if a sponsor chooses to represent its products in the best possible light. The commercialization of clinical trials has neither improved the quality of the science nor enhanced the protection of human research participants. The findings from this case

study suggest that additional protections for human research participants, including new approaches for the conduct, oversight, and reporting of industry-sponsored trials, are necessary. A clinical trials system in which sponsors fund the trials that are conducted by independent investigators would provide additional protections," the authors conclude.

Source: JAMA and Archives Journals