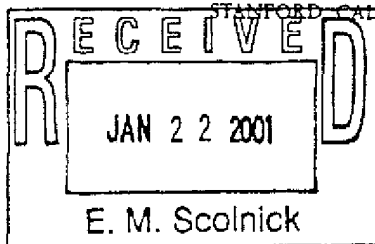




STANFORD UNIVERSITY MEDICAL CENTER

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COPY

January 9, 2001

Mr. Raymond Gilmartin  
Chief Executive Officer  
Merck and Co.  
One Merck Drive  
Whitehouse Station, New Jersey 08889

Dear Dr. Gilmartin,

A series of serious events involving certain employees of, and possibly a policy of, Merck & Co. has come to my attention rather accidentally and I wanted to relay these events which might have substantial implications and complications. The result is harmful to the traditionally very fine Merck public image and is counter-productive to the Vioxx sales effort. My perspective is that of the Principal Investigator of ARAMIS (Arthritis, Rheumatism, and Aging Medical Information System). This NIH-funded national data bank first identified and quantitated the stealth epidemic of NSAID gastropathy, quantitated differences in toxicity among NSAIDs, and ARAMIS investigators have worked hard for a long time to find and implement ways of reducing the frequency of serious GI adverse events with NSAIDs. I believe that the Cox-1 sparing agents are our best approach toward better drug safety in this area.

My accidental involvement: On Saturday October 28<sup>th</sup> I received a call at home from Dr. Louis Sherwood of Merck Pharmaceuticals. Dr. Sherwood complained that Dr. Gurkirpal Singh of our group had an anti-Merck bias and was giving lectures that were irresponsibly anti-Merck and specifically anti-Vioxx. Dr. Singh was held to have used a slide which depicted a person hiding data under the covers, had called Merck the "Firestone of the drug industry", and had requested data from Merck which was not appropriate for him to have. Dr. Sherwood suggested that if this continued Dr. Singh would "flame out" and there would be consequences for myself and for Stanford. Dr. Sherwood had previously called Dr. Judith Swain, Chair of our Department, and subsequently called Dr. Edward Harris, Chair of our Division, with similar complaints. I agreed to look into the matter and to take appropriate action and indicated that it is not our policy to bias any presentation in any direction. I asked him to provide me with full details of any such transgression that occurred after this date.

Anstice  
EXHIBIT NO. 123  
L. GOLKOW

I spoke with Dr. Singh and reviewed the slides of his presentation. The talk was mainly about the frequency and severity of NSAID Gastropathy and secondly about the advantages of the new Cox-1 sparing agents, of which Vioxx is one. Equal numbers of slides were devoted to Celebrex and to Vioxx. The talk was strongly in favor of broad use of the new Cox-1 sparing agents. Data were mainly from the standard studies, although three slides were from a presented but not yet published randomized renal toxicity study of Celebrex and Vioxx by Andrew Whelton comparing side-by-side renal and cardiovascular toxicity which was not in favor of Vioxx. The little man under the covers was not in the sequence, having been removed when Dr. Singh succeeded in getting the requested data (again not favorable to Vioxx), from Merck. Dr. Singh clearly did not understand the "Firestone" reference and indicated that he had not made the statement. I asked Dr. Singh to be certain to be rigorously balanced in future presentations and he agreed, although stressing that he had also been balanced in the past. I talked with three people who had been in Dr. Singh's audience; one thought the presentation contained humor directed at Merck but that the data were balanced and the other two found the presentations completely unremarkable.

The much broader issues, which surfaced at the American College of Rheumatology meetings, were most disturbing and involve suppression of data by Merck and a consistent pattern of intimidation of investigators by Merck staff, principally Dr. Sherwood but also others on his staff.

A number of physicians have concerns that Vioxx may have some serious and under-emphasized drug toxicity problems, particularly at the 50 mg dose approved for pain control—these concerns are shared by the FDA renal reviewer. Vioxx has been reported to have more frequent peripheral edema problems, more aggravated hypertension, more congestive heart failure, and more heart attacks than other NSAIDs, especially Celebrex. Some 0.4 % of Vioxx subjects had heart attacks compared with 0.1 % in the naproxen arm in the Merck-sponsored VIGOR study and this was statistically significant. Some of these data have been described in the Wall Street Journal and may have affected stock prices but there has been little information presented to date in the medical literature. Merck presented two posters on the VIGOR trial at the recent ACR meetings which did not contain data on the side effects of interest; the posters were very well attended, with everyone wanting to know about the data on these points, but it was not available. I tried unsuccessfully to get the data myself; it is hard to judge these areas without the numerical details. Yet, one could not avoid the conclusion that because of the interest in these issues the data would have been presented had they been favorable. There was a lot of muttering and a lot of people with concerns. The publication of the VIGOR trial recently in the NEJM did not contain the data on edema and fluid retention at all, and dismissed the heart attack data with weak arguments.

Even worse were the allegations of Merck damage control by intimidation, often with a pattern of going to the Dean or Department Head with complaints of anti-Merck bias and always alleging unbalanced anti-Vioxx presentations. This has happened to at least eight investigators: Dr. Singh; Dr. Peter Lipsky, now research chief at the Arthritis Institute;

Dr. Andrew Whelton of Hopkins; Dr. Michelle Petri of Hopkins; Dr. David Yocum of Tucson, currently head of the FDA advisory panel; Dr. Lee Simon of Harvard; Dr. James McMillen; and Dr. Thomas Stillman. I suppose I was mildly threatened myself, although I have never spoken or written on these issues.

I documented the intimidation of the individuals listed above by personally speaking with each of them. Dr. Simon believes that one of his two academic appointments has been jeopardized. Dr. McMillen believes that his VCF appointment at Hershey was revoked because of these accusations. Dr. Petri had a speaking engagement unprofessionally cancelled by Merck and an unrenowned speaker substituted; he was also bothered by phone calls from Merck persons alleging unbalanced presentations. Dr. Singh had a speaking engagement cancelled and the audience was told that he had been fired. Dr. David Yocum had similar experiences. Dr. Lipsky, while at Southwestern, was forced to do a slide by slide justification of a CME program felt to be critical of Vioxx. These are respected investigators with long experience and high integrity. I also spoke with several past Merck employees who asked to remain anonymous but who confirmed the existence of a pattern of intimidation through the Department Chairs or the equivalent, often with the hint of loss of Merck funding to the institution.

An ironic result of all this is that Vioxx is getting more scrutiny of its salt and water toxicity than if the data had been clearly presented, and Merck is taking a big public relations hit among rheumatologists. The investigators whose balance was criticized are prominent and several advise the FDA—a role not often given to unbalanced presenters. In the view of most rheumatologists including myself, Vioxx (and Celebrex) represent a major medical advance in terms of improving GI safety, which is the dominant toxicity of NSAIDs and is the most common serious adverse event of NSAIDs. These drugs should on balance, save a substantial number of lives. The fluid retention and related problem data are actually not all that bad, and the cover-up is a worse problem than the side effects of fluid retention and hypertension and CHF, which could be handled by stronger labeling for at risk patients, or by other means. Else, there is a risk of case reports of seriously complicated congestive heart failure or other serious adverse reactions, which could threaten the drug approval. The heart attack data, of course, need to be confirmed or refuted by further study, as do the data on comparative renal toxicity between Cox-1 sparing agents.

I spoke with Dr. Sherwood at length on November 22 and aired the above concerns directly. He defended by saying that Merck was a great company and, therefore, could not be doing anything inappropriate. He said that he had been with Merck for 13 years and had never noticed anything that was not appropriate. He noted that he had previously been a Department Chair and that he knew what was appropriate and what was not, and that he knew how to get things done through the network. He said that if he heard about something that was alleged to be anti-Vioxx that it was his right to call anyone he wanted to about it. When told that each of the investigators maintained that presentations had been balanced he said he didn't want to get into "he said, she said" kinds of discussions. He said that there weren't any problems with the drug and that anyway they only occurred at high dose. When told that an ex-Merck employee had quoted him as saying

"we only have three problems, Whelton, Simon, and McMillen, and Simon has been taken care of" there was a long pause and then he said that he "did not remember" saying that. When told that while both I and the people I had talked with had often had differences in viewpoint with one or another drug firm, none of us had ever heard of harassment of investigators through their institutions he did not have a response but said that he "heard me."

From the discussions above I make three conclusions. First, some investigators at some times probably do make statements that may seem seriously unbalanced to those vested or instructed in opposite opinions and that close attention to strict impartiality is essential for any person making presentations on any such subject. Second, Merck has been attempting to systematically downplay some unusual side effect patterns of Vioxx. I would hesitate to use the term "hiding data" but Merck has certainly not been forthcoming with data and has made access to the data difficult. Finally, and most importantly, Merck employees have systematically attacked those investigators or speakers who expressed what Merck staff felt were critical opinions in a manner which seriously impinges on academic freedom.

I believe that these are serious matters and that Merck should take care of them internally, in its own interest, and in the interest of patients. I will appreciate your response to the issues raised here and to learning about actions which have been taken.

Sincerely,



James F. Fries, M. D.  
Professor of Medicine

cc: Mr. David Anstice, President Merck U. S. Human Health  
Dr. Ed Skolnick, President Merck Research Labs