Jonathan M. Edelman, M.D.
Executive Director, Global Center for Scientific Affairs
Merck Research Laboratories

August 18, 2008

An Open Letter to the Editors of *The Annals of Internal Medicine*

In this open letter to the editors of *The Annals of Internal Medicine,* Merck would like to put in perspective the latest article by four authors who served as paid consultants to plaintiffs' lawyers in the VIOXX litigation against Merck. We are troubled by the biased article, which contains numerous inaccuracies, and wonder about the motivation behind this attack on Merck's scientific excellence and integrity.

It is unfortunate that the authors and journal editors chose not to contact Merck before finalizing these publications. Had any of these individuals contacted Merck, factual errors could have been avoided.

The ADVANTAGE clinical trial was designed, conducted, analyzed, interpreted and published by the scientific department of Merck's U.S. Human Health (USHH) organization, Clinical Development (CDP), in conjunction with participating investigators. CDP was part of the Medical and Scientific Affairs department of USHH and was separate from the marketing department within USHH.

In the article, the authors erroneously claim that the objectives of the ADVANTAGE study were not scientific, and base this spurious conclusion on their review of a limited selection of documents produced in the VIOXX litigation. The authors appear to purposely fail to distinguish between the various departments of Merck's USHH organization, including its scientific research and marketing departments.

There's no doubt that the ADVANTAGE clinical trial had a legitimate scientific purpose. That purpose was to assess the gastrointestinal tolerability of VIOXX compared to naproxen – a commonly used arthritis medicine with known tolerability problems – in the treatment of patients with osteoarthritis in a primary care setting, and for the first time allowed patients taking concomitant aspirin to participate.

ADVANTAGE was a double-blind, randomized, controlled clinical trial with a legitimate scientific purpose designed to answer previously unanswered questions about the use of VIOXX in osteoarthritis in a primary care setting. It was not a seeding study.

The study assessed GI tolerability by seeing whether VIOXX or naproxen, at the highest approved doses for long-term treatment of osteoarthritis, caused fewer adverse events like abdominal pain, epigastric discomfort, diarrhea, heartburn, nausea, and dyspepsia.

ADVANTAGE was important because although the earlier VIOXX clinical trial program provided extensive data on efficacy and safety, it did not include naproxen as a comparison medication, and did not conduct research in the primary care setting, where patients with osteoarthritis would likely be seen by physicians who would consider VIOXX as a treatment option.

In addition, ADVANTAGE was the first study of VIOXX conducted by Merck that allowed the concomitant use of aspirin by patients participating in the trial. Indeed, the very journal that published the article that is the subject of this letter previously published the results of the ADVANTAGE study back in 2003, and at the time acknowledged that physicians would be interested in the type of results ADVANTAGE produced.

In the end, ADVANTAGE showed a different gastrointestinal profile between VIOXX and naproxen that was unaffected by concomitant use of aspirin. This was an important medical result for physicians. In addition to measuring the GI tolerability of VIOXX, investigators also monitored patients for adverse events, which were required to be submitted to the FDA. Therefore, in ADVANTAGE, Merck was further evaluating any potential risks of VIOXX.

It is important to emphasize that ADVANTAGE met all the Merck requirements for clinical research. All studies sponsored by Merck must have a protocol that describes the scientific, administrative, and regulatory aspects of the study in a manner that is consistent with currently accepted scientific methodology, FDA's Good Clinical Practice guidance and worldwide regulatory requirements.

We also want to underscore that the scientific purpose of ADVANTAGE was properly disclosed to physicians-investigators, participants, and institutional review boards, and Merck's business interests were clearly understood. As is always the case, a scientifically sound and properly conducted study that further demonstrates the benefits of a drug would have a favorable impact on patients with debilitating arthritis, doctors searching for ways to treat their pain, and the pharmaceutical company that produced the drug. Such studies also further our understanding of the drug's potential risk.

Merck firmly believes there is great value in understanding questions physicians want answered and in conducting rigorous, scientific clinical studies to address those questions. We believe we acted appropriately with respect to the ADVANTAGE trial, and stand behind our strong beliefs in the principles of scientific integrity. In publishing the paper and accompanying editorial in question, without further investigating readily available information, we believe that the Annals failed to act in the best interests of their readers or the scientific community.

Sincerely,

Jonathan M. Edelman, M.D.
Executive Director, Global Center for Scientific Affairs
Merck Research Laboratories