DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: February 28, 2007

TO: Randall W. Lutter, Ph.D.
Associate Commissioner for Policy and Planning
Food and Drug Administration

THROUGH: Vince Tolino
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

FROM: Igor Cerny, Pharm.D. /s/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

SUBJECT: Conflict of Interest Waiver for Robert Levine, M.D.

I am writing to request a waiver for Robert Levine, M.D., a temporary voting member of the Arthritis Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. §208(a). The appointing official may grant waivers under section 208(b)(3) where "the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved" and where the individual has made a disclosure of the financial interests at issue. We have determined that you are the appointing official for purposes of section 208. Therefore, you have the authority to grant Dr. Levine a waiver under 18 U.S.C. §208(b)(3).

Section 208(a) prohibits Federal executive branch employees, including special Government employees, from participating personally and substantially in matters in which the employee, or any other person whose interests are imputed to the employee under 18 U.S.C. §208, has a financial interest. Since Dr. Levine is a special Government employee, he is under a statutory obligation to refrain from participating in an official capacity in any particular matter having a direct and predictable effect on a financial interest attributable to him, his spouse, minor child, or general partner; an organization or entity for which he serves as an officer, director, trustee, general partner, or employee; and, a person with whom he is

negotiating for, or has an arrangement concerning, prospective employment.

Dr. Levine has been asked to participate in all official matters concerning the safety and efficacy of New Drug Application (NDA) 21-389/21-772, proposed trade name, Arcoxia (etoricoxib), a non-steroidal, anti-inflammatory, cyclooxygenase-2 (COX-2) enzyme inhibitor, manufactured by Merck & Company, Inc., for the proposed indication of the relief of the signs and symptoms of osteoarthritis. This matter is a particular matter involving specific parties.

The function of the Arthritis Advisory Committee, as stated in its Charter is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of arthritis, rheumatism, and related diseases, and to make appropriate recommendations to the Commissioner of Food and Drugs.

Dr. Levine has advised the Food and Drug Administration that he has a financial interest that could potentially be affected by his participation in the matter at issue. **Dr. Levine owns stock in———— sponsor of————**

As a temporary voting member of the Arthritis Drugs Advisory Committee, Dr. Levine potentially could become involved in matters that could affect his financial interest. Under 18 U.S.C. §208(a), he is prohibited from participating in such matters. However, as noted above, you have the authority under 18 U.S.C. §208(b)(3) to grant a waiver permitting Dr. Levine to participate in such matters as you deem appropriate.

For the following reasons, I believe that it would be appropriate for you to grant a waiver to Dr. Levine that would permit him to participate in the matter previously described.

First, Dr. Levine's interest in——— is not so substantial in relation to his total net worth as to preclude his participation in this matter. Dr. Levine's stock interest in ——— represents less than —% of his total net worth.

Second, it is unlikely that Dr. Levine's participation in the matter at issue would have a substantial affect on his interest in———. Even if it is possible that———— stock could be affected because of the committee's recommendations and the Agency's action concerning————————————, the

financial impact on ——— would likely be minimal. ——— is a large, diverse company that develops, manufacturers, and markets a large number of products. ——— does not depend on one or two products for its economic survival.

Third, the uniqueness of Dr. Levine's qualification justifies granting this waiver. The advisory committee will be considering the safety and efficacy of a novel COX-2 selective, non-steroidal, anti-inflammatory drug (NSAID). This represents the first novel drug of this class considered for marketing in the U.S. since the withdrawals of Vioxx and Bextra. The safety database to assess cardiovascular, renovascular, and gastrointestinal safety consists of data from more than 35,000 patients, a safety database unprecedented for consideration at the time of the initial NDA for a drug in this class. A meaningful discussion of the efficacy and safety data will require contributions from multiple disciplines including gastroenterology. The overall risk assessment discussion will be informed by contributions from the members of the Drug Safety and Risk Management committee. Because of this, the Division of Arthritis, Anesthetic and Rheumatology Products (DAARP) feels it would be pertinent to have a panel of experts, to include, when possible more than one expert in a particular area, to consider a wider perspective and account for all aspects of the product under review. In an attempt to gain the appropriate representation, DAARP and Advisors and Consultants Staff (ACS) contacted 11 individuals listed as current SGEs and/or Federal Employees of the National Institutes of Health. Of the eleven gastroenterologists contacted, four accepted the offer to represent the agency's interests, most declining due to a scheduling conflicts and prior commitments. Of the four, two of the interested parties disclosed conflicts of a significant nature, resulting in recusal. As mentioned above, the division is interested in gaining the perspective of more than one expert in an effort to remain objective and in doing so requests that a waiver be granted for Dr. Levine to participate as there has been a genuine effort to secure individual participation and representation with minimal conflict of interest.

Dr. Levine's background, breadth of knowledge, and experience with the issues associated with NSAIDs, including COX-2 selective NSAIDs, make him uniquely qualified to participate on this advisory committee meeting. As noted above, the effects of COX-2 selective inhibitors and traditional NSAIDs on gastrointestinal outcomes have found that upper gastrointestinal clinical events may present the potential for GI Injury. Dr. Levine's clinical experience as a

gastroenterologist with experience in endoscopy and mucosal injury as well as his clinical trial background allow him to speak to the potential for GI injury as it relates to the product being considered and allow him to accurately and appropriately assess the data presented from the trials. The difficulty of locating a similarly qualified individual without a disqualifying financial interest to serve on the committee has been addressed above and the division feels that Dr. Levine should be granted a waiver to fully participate in the upcoming meeting.

Finally, the Federal Advisory Committee Act requires that committee memberships be fairly balanced in terms of the points of view represented and the functions to be performed by the advisory committee. Also, the committee's intended purpose would be significantly impaired if the Agency could not call upon experts who have become eminent in their fields, notwithstanding the financial interests and affiliations they may have acquired as a result of their demonstrated abilities. Dr. Levine is Professor of Medicine, Division of Gastroenterology, at the State University of New York. He is board certified in gastroenterology and internal medicine. Dr. Levine has authored 88 peer-reviewed publications and several book chapters. In addition, Dr. Levine has served as an Editorial Board Member for the *Annals of Internal Medicine,* the journal *Hepatology,* and the *International Journal of Molecular Medicine.* He is also a member of numerous professional societies, such as the American Gastroenterology and the American Federation for Clinical Research. I believe that Dr. Levine's participation will contribute to the diversity of views and expertise represented on the committee and will help provide a foundation for developing advice and recommendations that are fair and comprehensive.

Accordingly, I recommend that you grant Dr. Robert Levine a waiver that will permit him to participate in all official matters concerning the safety and efficacy of New Drug Application (NDA) 21-389/21-772, proposed trade name, Arcoxia (etoricoxib), a non-steroidal, anti-inflammatory, cyclooxygenase-2 (COX-2) enzyme inhibitor, manufactured by Merck & Company, Inc., for the proposed indication of the relief of the signs and symptoms of osteoarthritis. I believe that such a waiver is appropriate because in this case, the need for the services of Dr. Levine, outweighs the potential for a conflict of interest created by the financial interests attributable to him.

CONCURRENCE: /s/ 3/14/07

Vince Tolino
Director, Ethics and
Integrity Staff
Office of Management Programs
Office of Management

Date

DECISION:

X Waiver granted based on my determination, made in accordance with section 18 U.S.C. §208(b)(3), that the need for the individual's services outweighs the potential for a conflict of interest created by the financial interest attributable to the individual.

_____ Waiver denied.

/s/ 3/16/07

Randall W. Lutter, Ph.D.
Associate Commissioner for Policy
and Planning
Food and Drug Administration

Date