MEMORANDUM

DATE: June 11, 2007

TO: Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy
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 John R. Teerlink, M.D.

I am writing to request a waiver for John R. Teerlink, M.D., a member of the Cardiovascular and Renal Drugs Advisory Committee advising the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees, from the conflict of interest prohibitions of 18 U.S.C. §208(a). Waivers under section 208(b)(1) may be granted by the appointing official where "the [financial] interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such employee" 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 John R. Teerlink, M.D., a waiver under section 208(b)(1).

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. Teerlink is a full-time 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. Teerlink has been asked to participate in the discussions of the cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline. This matter is coming before a joint meeting of the Endocrinologic and Metabolic Drugs and the Drug Safety and Risk Management Advisory Committees. This meeting is a particular matter involving specific parties.

The functions of the Endocrinologic and Metabolic Drugs Advisory Committee 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 endocrine and metabolic disorders and to make appropriate recommendations to the Commissioner of Food and Drugs.

The function of the Drug Safety and Risk Management Advisory Committee is to advise the Commissioner of Food and Drugs on risk management, risk communication, and quantitative evaluation of spontaneous reports for drugs for human use and for any other product for which the Food and Drug Administration has regulatory responsibility. The committee also advises the Commissioner of Food and Drugs regarding the scientific and medical evaluation of all information gathered by the Department of Health and Human Services and the Department of Justice with regard to safety, efficacy, and abuse potential of drugs or other substances, and recommends actions to be taken by the Department of Health and Human Services with regard to the marketing, investigation, and control of such drugs or other substances.

Dr. Teerlink has advised the Food and Drug Administration that he has financial interests which could potentially be affected by his participation in the matter described above. **Dr. Teerlink serves as a blinded endpoint reviewer for the ———— in heart failure ———— ———— clinical trial, sponsored by ———— ————. The purpose of this study is to determine whether ———— is superior to placebo in reducing mortality and cardiovascular morbidity, defined as the occurrence of death from any cause or hospitalization due to cardiovascular disease, in subjects with heart failure ————. ———— is the sponsor of ————, competing product to Avandia, Avandamet, and Avandaryl.**

Dr. Teerlink also owns a moderate number of shares in a health sector mutual fund. This fund represents less than —% of his total net worth.

As a member of the Cardiovascular and Renal Drugs Advisory Committee advising the Endocrinologic and Metabolic Drugs and Drug Safety and Risk Management Advisory Committees, Dr. Teerlink potentially could become involved in matters that could affect his financial interests. 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)(1) to grant a waiver permitting Dr. Teerlink 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. Teerlink that would permit him to participate in the matter described above.

First, it is significant to note that Dr. Teerlink's consulting is unrelated to the issue coming before the committees.

Second, with respect to Dr. Teerlink's financial interest in a health sector mutual fund, it is important to consider that he has no influence over the specific investments in fund or the strategies that are employed by the fund manager. It is also important to consider that this fund represents a small portion of his total net worth.

Third, the uniqueness of Dr. Teerlink's qualification justifies granting this waiver. The upcoming meeting is intended to discuss cardiac ischemic/thrombotic risks of thiazolidinediones, particularly rosiglitazone. This meeting will include experts in the field of cardiology. Clinical data to be discussed include a meta-analysis of controlled clinical trials and several large clinical outcome trials involving rosiglitazone. Dr. John Teerlink is one of two cardiologists identified with expertise that is critical to the subject for discussion before the advisory committee on July 30, 2007. At issue is the finding of a 40% increase in cardiac ischemic events in a population of patients with type 2 diabetes mellitus who are treated with Avandia (rosiglitazone) based on a pooling of 42 short-term clinical trials. Dr. Teerlink's experience in clinical medicine, basic research, and clinical investigation of heart failure

provides a unique perspective on this finding and its impact on public health as well as individual patient care.

Lastly, the difficulty in locating a similarly qualified individual without a disqualifying financial interest to serve on the committee also justifies this waiver. The Division of Metabolism of Endocrinology Products consulted the Division of Cardiovascular and Renal Drug Products, seeking advice on members from the Cardiovascular and Renal Drugs Advisory Committee, who would provide valuable experience and scientific knowledge to the subject matter. A total of 10 cardiologists with subspecialty interest relevant to this subject matter were considered. Of those available for the date of July 30, 2007, all but one had a conflict of interest or had to be recused from participation. This one individual has expertise in arrhythmias not cardiac ischemic risk.

Further, 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. This meeting will include a discussion of retrospective adjudication of cardiac events in a meta-analysis for which Dr. Teerlink's knowledge of this disease process will help the committees better understand the strengths or limitations of that analysis. While this meeting will focus more on the cardiac ischemic risk associated with rosiglitazone therapy, this drug and others in the class are associated with heart failure development and exacerbation. The risk of cardiac ischemia from the meta-analysis was notable in a 52-week study of patients with Class 1 and 2 heart failure. The cardiac ischemic events adjudicated in this study were not from an endpoints committee but by individual investigators. Dr. Teerlink's expertise as a heart failure specialist and his involvement in the conduct of large, heart failure studies are critical to the interpretation of the findings from this study as well as other studies included in the meta-analysis. Furthermore, Dr. Teerlink's previous experience with FDA's cardiorenal advisory committee meetings enables an understanding of the process and meeting conduct that will better advise the agency on its decision regarding this drug. I believe that

Dr. Teerlink will bring an enormous amount of experience and knowledge that is critical to the committees' discussions and his participation will help provide a foundation for developing advice and recommendations that are fair and comprehensive.

Accordingly, I recommend that you grant John R. Teerlink, M.D., a waiver that will permit him to participate in all official matters concerning the discussions of the cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline. I believe that in this case, Dr. Teerlink's financial interests are not so substantial as to be deemed likely to affect the integrity of the services that the Government may expect from him.

CONCURRENCE: /s/ 6/22/07

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)(1), that the interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from such employee.

_____ Waiver denied.

/s/ 6/29/07

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

Date