DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

DATE: June 21, 2007

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

THROUGH: Michael F. Ortwerth, Ph.D.
Deputy Director, Advisory Committee
Oversight and Management Staff

FROM: Susan Peters /s/
Lead Public Health Analyst
Advisors and Consultants Staff
Center for Drug Evaluation and Research

SUBJECT: Conflict of Interest Waiver for Steven Nissen, M.D.

I am writing to request a waiver for Steven Nissen, M.D., a temporary non-voting member of the Endocrinologic and Metabolic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. §208(a). Waivers under section 208(b)(3) may be granted by the appointing official 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 Steven Nissen, M.D., 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. Nissen 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 as an arrangement concerning, prospective employment.

Dr. Steven Nissen has been invited to answer questions regarding a meta-analysis of pooled data from 42 clinical studies of rosiglitazone that was published in the June 14, 2007, issue of the *New England Journal of Medicine*. The committees will be discussing 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 function 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.

Dr. Nissen has advised the Food and Drug Administration that he has financial interests that could potentially be affected by his participation in the matter at issue. **Dr. Nissen is Chairman of the Department of Cardiovascular Medicine at Cleveland Clinic. An academic research organization within his department, the Cleveland Clinic Cardiovascular Coordinating Center, was awarded research grants by ——— to conduct a meta-analysis of clinical studies of ——————— for cardiovascular outcomes and a separate clinical study on the drug's effect on coronary artery disease. Dr. Nissen does not direct the meta-analysis but does serve as the Principal Investigator (PI) for the study on the ——————— effect on coronary artery disease. According to Dr. Nissen, he does not receive any personal remuneration from the grants. ——————— is a ——————————— competing product to rosiglitazone.**

In addition, the Cleveland Clinics Cardiovascular Coordinating Center has pending research grants with ——— and ——— to conduct clinical studies related to the thiazolidinediones. According to Dr. Nissen, he will not serve as an investigator for the studies nor will he receive any personal remuneration from the grants.

Further, the Cleveland Clinic Cardiovascular Coordinating Center has received research funding from ——— and ———, firms that make competing products to the thiazolidinediones. These funds are for clinical trials of products unrelated to the thiazolinediones and their competitors. Dr. Nissen's involvement is solely administrative as Director of the Department of Cardiovascular Medicine. Dr. Nissen's employer's interests in these firms are unrelated to the issues to be discussed and the affected products. Arguably, his interests do not constitute a financial interest in the matter under 18 U.S.C. § 208(a). Nevertheless, in the utmost of caution, I recommend that this wavier be granted.

As a temporary non-voting member of the Endocrinologic and Metabolic Drugs Advisory Committee, Dr. Nissen 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)(3) to grant a limited waiver permitting Dr. Nissen to answer questions directly related to his publication and meta-analysis. He will not be allowed to participate in any of the committees' discussions, deliberations, or voting with respect to the cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline.

First, although Dr. Nissen's employer currently has financial interests in ———, ——— ———, and ———, he himself has no personal financial interest in the firms or their products. Generally, there is less likelihood that the judgment of the individual will be affected by an imputed interest of an employer than by a personal financial interest.

Second, it is unlikely that Dr. Nissen's participation in this meeting will have a direct and predictable impact on

his employer's research studies sponsored by ——— ———, ———————————, and ———. Even if it were possible that these firms would be more or less likely to continue to provide financial support to the Cleveland Clinic in the future as a result of the committees' deliberations, the financial impact would probably be relatively insignificant since these are not significant financial interests. The Cleveland Clinic is a large, diverse, research institution that receives funding from a variety of public, private, and governmental agencies in support of its research activities. It does not depend upon one or two sources for its funding. It is unlikely that the funding from ———————, ——————— ———————, and ——— represents a substantial portion of the Clinic's total research budget. In 2004, the Cleveland Clinic Foundation received over ——————— in funding from a variety of public, private, and governmental agencies in support of its research activities.

Third, the uniqueness of Dr. Nissen's qualification justifies granting this waiver. According to the review Division, Dr. Nissen is uniquely qualified to answer questions regarding his meta-analysis of pooled data from 42 clinical studies of rosiglitazone that was published in the June 14, 2007, issue of the *New England Journal of Medicine*. Dr. Steven Nissen is the Chairman of the Department of Cardiovascular Medicine. The meta-analysis was funded and conducted under his direction by the academic research organization, the Cleveland Clinic Cardiovascular Coordinating Center, within the Department of Cardiovascular Medicine. Dr. Nissen is board certified in internal medicine and cardiovascular medicine and is a professor of medicine at the Ohio State University. Dr. Nissen is also an elected member of the American College of Cardiology Board of Trustees and several other ACC committees. He serves on the editorial board of nine scientific publications, including the International Journal of Cardiac Imaging, Cardiology Today and Clinical Cardiology. Dr. Nissen has played an important role in numerous clinical trials, and he lectures frequently on the use of intravascular ultrasound and has authored several dozen book chapters and more than 100 articles in scientific journals such as Circulation, the Journal of the American College of Cardiology and the American Journal of Cardiology, demonstrating his vast clinical and research expertise in acute myocardial infarction, unstable angina, and atherosclerosis. His expertise in the field of

cardiology and vast clinical trial experience with cardiovascular drugs will provide much needed insight on this difficult topic.

In addition, any conflict or appearance of a conflict will be mitigated further by the fact that the Agency has decided to limit Dr. Nissen's participation to answering questions regarding his meta-analysis of pooled data from 42 clinical studies of rosiglitazone that was published in the June 14, 2007, issue of the *New England Journal of Medicine*. Under the terms of this limited waiver, he will not be allowed to participate in the committees' discussions, deliberations, or voting with respect to the discussions on the cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline.

Accordingly, I recommend that you grant Steven Nissen, M.D., a limited waiver that will permit him to answer questions regarding a meta-analysis of pooled data from 42 clinical studies of rosiglitazone that was published in the June 14, 2007, issue of the *New England Journal of Medicine*. Under the terms of this limited waiver, he will not be allowed to participate in the committees' discussions, deliberations, or voting with respect to the discussions on the cardiovascular ischemic/thrombotic risks of the thiazolidinediones, with focus on rosiglitazone, as presented by the FDA and GlaxoSmithKline. I believe that

such a limited waiver is appropriate because in this case, the need for the services of Dr. Nissen outweighs the potential for a conflict of interest created by the financial interests attributable to him.

CONCURRENCE: /s/ 6/29/07
Vince Tolino Date
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

DECISION:

X Limited waiver granted based on my determination, made inaccordance 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.

_____ Limited waiver denied.

/s/ 6/29/07
Randall W. Lutter, Ph.D. Date
Deputy Commissioner for Policy
Food and Drug Administration