



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: May 14, 2008

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

THROUGH: Vince Tolino /5/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

Michael F. Ortwerth, Ph.D. /5/
Deputy Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Igor Cerny, Pharm.D. /5/
Director, Advisors and Consultants Staff
Center for Drug Evaluation and Research

SUBJECT: 208(b)(3) 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 to 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 Dr. Nissen a limited waiver under section 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 his employer has a financial interest. Because Dr. Nissen is a special Government employee, he is under a statutory obligation to refrain from participating in any deliberations that involve a particular matter having a direct and predictable effect on a financial interest attributable to him or his employer.

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. Steven Nissen has been invited to present and answer questions regarding the "Need for Cardiovascular Assessment during the Approval Process for Anti-diabetic Drugs" in the July 1-2, 2008, meeting. The committee will discuss the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

This matter is coming before a meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. This issue is a particular matter involving specific parties.

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 (C5), was awarded research grants by _____, _____, and _____ to conduct the following studies. According to Dr. Nissen, he has no direct involvement in these studies. He does not receive any personal remuneration or salary support. _____, _____, and _____ are affected firms of this meeting.

- _____ treatment on glomerular filtration rate (GFR) in patients with Type 2 diabetes, in comparison with _____ treatment. Study period is _____ to _____ and C5 receives approximately \$_____ per year.
- Study of the _____. C5 is adjudicating cardiovascular endpoints for this trial. Study period is _____.

- Adjudicating endpoints for studies of _____, an investigational _____. Study period is _____ to _____.

- Study of _____ and _____ in the prevention of _____ in subjects with _____. Study period is _____.

In addition, Dr. Nissen's employer, the Cleveland Clinics Cardiovascular Coordinating Center, has past and current contracts with _____, _____, _____, _____, _____, and _____ and is currently in negotiation with _____, _____ and _____ for studies. Dr. Nissen's employer's interests in these studies/firms are unrelated to the issues to be discussed and the affected products. Further, Cleveland Clinics Cardiovascular Coordinating Center has had past research grants with _____ and _____ that are related to the affected products of the meeting. Arguably, these unrelated and past interests do not constitute a financial interest in the matter under 18 U.S.C. § 208(a).

As a Temporary Non-voting Member to the Endocrinologic and Metabolic Drugs Advisory Committee, Dr. Nissen potentially could become involved in matters that could affect his financial interests. Under section 208, he is prohibited from participating in such matters. However, as noted above, you have the authority under section 208(b)(3) to grant a limited waiver permitting Dr. Nissen to present and answer questions regarding the "Need for Cardiovascular Assessment during the Approval Process for Anti-diabetic Drugs." He will not be allowed to participate in any of the committees' discussions, deliberations, or voting with respect to the role of cardiovascular assessment in the pre-approval and post-approval settings for drugs and biologics developed for the treatment of type 2 diabetes mellitus.

For the following reasons, I believe that it would be appropriate for you to grant a limited waiver to Dr. Nissen that would allow him to participate partially in the matter described because the need for his services greatly outweighs the conflict of interest created by these financial interests.

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, 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 2005, the Cleveland Clinic Foundation received over \$_____ in funding from a variety of public, private, and governmental agencies in support of its research activities.

Third, according to the Review Division, the uniqueness of Dr. Nissen's qualification justifies granting this waiver. Over the past few years, and recently after the rosiglitazone issue, there has been much public debate surrounding the need for cardiovascular outcomes data for an anti-diabetic agent. The debate is quite divided with advocates for such data arguing that requiring such studies will improve knowledge on the efficacy and safety of a drug. Critics of such a position have argued that the requirement of such costly clinical trials would slow down the availability of effective therapies targeting treatment of hyperglycemia, a surrogate that has direct impact on other complications in diabetes aside from cardiovascular risks. It is important to note that treatment of diabetes targets normal glycemic control to reduce many risks, microvascular and macrovascular. Over the past several decades, evidence that good glycemic control reduces the risk of microvascular complications such as kidney failure, blindness, and neuropathy is extensive from several large clinical trials.

Dr. Nissen is uniquely qualified to present and answer questions regarding the "Need for Cardiovascular Assessment during the Approval Process for Anti-diabetic Drugs." The committee discussion must take into consideration these very opposite views and it is anticipated that a

discussion of cardiovascular risk assessment through other means will be raised. The distinction of a cardiovascular risk assessment differs from a cardiovascular outcomes trial in that the latter focuses on evidence of clinical benefit whereas the former might focus on providing compelling evidence of no cardiovascular harm. Dr. Nissen has been instrumental in designing and conducting pre-approval trials that directly investigate cardiovascular effects of drugs ranging from diabetic therapies, anti-inflammatory therapies to cholesterol-lowering drugs. His scope of knowledge of imaging modalities as intermediate measures of efficacy will be an important contribution to the discussion on what level of evidence would be sufficient before concluding that a) cardiovascular outcome trial is required or b) there is little evidence of cardiovascular harm to preclude relying on glycemic control for approval. I believe that participation by Dr. Nissen in the committee's deliberations will contribute to the diversity of opinions and expertise represented on the committee.

Lastly, locating qualified individuals without disqualifying financial interest to serve on this advisory committee has been very difficult. Dr. Nissen is invited as a guest speaker, not a participant in the meeting. He will be one of six guest speakers and only one of two cardiologists. The topic of discussion is cardiovascular risk assessment in the approval process for anti-diabetic agents. This meeting touches not only on the approval of therapies for diabetes management but on cardiovascular risk in this patient population, interventions to reduce this risk, and complex study designs. As such, the meeting will require the participation of a multi-disciplinary committee including endocrinologists/diabetologists, cardiologists, and biostatisticians. The Division reviewed the qualifications of Special Government Employees (SGEs) from the Cardiovascular and Renal Drugs Advisory Committee and several of these members have already been invited to serve as committee members for this meeting. Two SGEs have the specific expertise as clinical trialists for cardiovascular outcomes trials to provide expert presentations as guest speakers to the committee members. The other guest speaker with expertise in cardiovascular outcomes trials also requires a waiver to present during the meeting.

Moreover, 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. Steven Nissen is Chair of the Cardiology at the Cleveland Clinic and has also served as chair for the Cardiovascular and Renal Drugs Advisory Committee. Dr. Nissen is board certified in internal medicine and cardiovascular medicine and is a professor of medicine at the Case Western Reserve University. Dr. Nissen is also an elected member of the American College of Cardiology (ACC) 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. He has also been the principal investigator in numerous clinical trials/investigations in which the endpoint of interest is relevant to this advisory

