



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 /s/
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

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

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

SUBJECT: 712(c)(2)(B) Conflict of Interest Waiver for Robert Califf, M.D.

I am writing to request a waiver for Robert Califf, M.D., a Temporary Non-voting Member of the Endocrinologic and Metabolic Drugs Advisory Committee, from the conflict of interest prohibitions of section 712(c)(2)(A) of the Federal Food, Drug, and Cosmetic Act. Waivers under section 712(c)(2)(B) may be granted by the appointing official where it is "necessary to afford the advisory committee essential expertise" and where the individual has made a disclosure to FDA of the financial interests at issue. We have determined that you are the appointing official for purposes of section 712(c)(2)(B). Therefore, you have the authority to grant Dr. Califf a limited waiver under section 712(c)(2)(B).

Section 712(c)(2)(A) prohibits Federal executive branch employees, including special Government employees, from participating in any particular matter in which the employee or an immediate family member has a financial interest that could be affected by the advice given to the FDA with respect to the matter. Because Dr. Califf 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.

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. Robert Califf has been invited to present and answer questions regarding the "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes" 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. Califf has advised the Food and Drug Administration (FDA) that he will be consulting with _____ on a trial assessing the impact of _____ on cardiovascular events. The first meeting is anticipated to be in late May 2008. Also, Dr. Califf is a consultant to _____ and serves on their Cardiovascular Metabolic (CVM) Council, which is a group of leaders who evaluate the _____ portfolio in cardiovascular and metabolic diseases. All consulting income is donated to non-profit organizations, with the majority going to the clinical research fellowship fund of the Duke Clinical Institute.

_____ and _____ are affected firms of this meeting.

As a Temporary Non-voting Member to the Endocrinologic and Metabolic Drugs Advisory Committee, Dr. Califf could become involved in matters that could affect his financial interest. Under section 712(c)(2)(A), he is prohibited from participating in such matters. However, as noted above, you have the authority under section 712(c)(2)(B) to grant a limited waiver permitting Dr. Califf to participate in such matters if necessary to afford this committee essential expertise. Dr. Califf will present and answer questions regarding the "Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes." 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. Califf that would allow him to participate partially in the matters described because his non-voting participation is necessary to afford the committee essential expertise.

First, although Dr. Califf currently has consulting activities planned with _____ and _____ he has wide variety of other unrelated consulting activities with many companies. Only a modest fraction of his overall activities is on behalf of any single company. To further mitigate his consulting interest, Dr. Califf donates all the fees received from pharmaceutical companies to not-for-profit charities.

Second, according to the Review Division, the uniqueness of Dr. Califf'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.

Of recent, several individuals have publicly called for the conduct of cardiovascular outcomes trials in the evaluation of anti-diabetic drugs. It is not clear whether these individuals understand what it takes to conduct such a trial to casually assert that this is feasible with every anti-diabetic drug. In fact, this is one of the driving reasons for holding this advisory committee to inform the public of these matters.

As a clinical trialist and a cardiologist who has had firsthand experience in many different roles and responsibilities in the conduct of large cardiovascular outcomes trials, it is without doubt that he is the best qualified to speak at this advisory committee meeting for the topic titled, “Challenges in Designing a Cardiovascular Outcomes Trial in Patients with Type 2 Diabetes”. Dr. Califf will not only recognize the economic burden of these trials but more importantly he will be able to inform the panel members as the magnitude of site recruitment, investigator selection and personnel training, working with Institutional Review Boards, patient recruitment, selection, and retention. Most notable is Dr. Califf’s vast experience with conducting clinical trials internationally. In this day and age, it is highly unlikely that clinical cardiovascular outcomes trial will only take place within the boundaries of the United States or North America. Dr. Califf has been specifically selected to speak at this meeting because of his extensive experience with implementing and executing trials within the United States and throughout the world. Advisory committee members will need to be informed of this fact and inquire of Dr. Califf the potential impact of foreign studies or foreign sites embedded within a clinical trial as it deliberates on whether cardiovascular outcomes trial should be a requirement in the approval of anti-diabetic drugs.

It should be emphasized that Dr. Califf is not being called upon to speak about one particular trial. Other speakers will cover results of previously conducted studies and studies that are ongoing in the diabetic patient population. Dr. Califf is being asked to focus on the “challenges of trial design” in general and will not be given the opportunity to campaign or call for support for any investigations he is directly involved in.

Lastly, locating qualified individuals without disqualifying financial interest to serve on this advisory committee has been very difficult. Dr. Califf is invited as a speaker only, not a participant in the meeting. 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 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. However, only two SGEs have the expertise as clinical trialists in cardiovascular outcomes trials to provide expert presentations as speakers to the committee members. The other speaker who has expertise in cardiovascular outcomes trials also requires a waiver to present during the meeting.

