DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: March 19, 2007

TO: Randall 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 Harrington, M.D.,

I am writing to request a waiver for Robert Harrington M.D., a member of the Cardiovascular and Renal 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. Harrington this 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. Harrington 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. Harrington has been asked to participate in all official matters concerning Supplemental New Drug Application (NDA) 20-758/S-037, Avalide (irbesartan/HCTZ), sponsored by Bristol Myers Squibb and Sanofi-Synthelabo, a subsidiary of Sanofi-Aventis, for use in the treatment of hypertension in patients unlikely to achieve blood pressure goals on one drug. This matter is coming before the Cardiovascular and Renal Drugs Advisory Committee and is a particular matter involving specific parties.

The function of the Cardiovascular and Renal Drugs 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 cardiovascular and renal disorders and to make appropriate recommendations to the Commissioner of Food and Drugs.

Dr. Harrington has advised the Food and Drug Administration that he and his employer have financial interests, which could potentially be affected by his participation in this matter. **Dr. Harrington is an ad hoc consultant to ————————, ———————— (joint venture) and ————————. In the past 12 months, he has consulted on matters unrelated to Avalide and its competing products. Although he has no consulting currently scheduled, he expects to consult for these firms this year and anticipates receiving nominal compensation. Any compensation will be directly donated to educational charities. ———————— and ————————, a subsidiary of ————————, are the sponsors of ———— and ——— makes several competing products.**

In addition, Dr. Harrington is Director of Cardiovascular Clinical Trials at the Duke Clinical Research Institute (DCRI). **The DCRI is participating in ———————————————— ———————————————— ———————————— study. This a large-scale, multi-center study to compare the effects of ——— with that of ———— plus diuretic ———————— on cardiovascular mortality and morbidity when used as first-line treatment for**

hypertension. The study period is January 2002 to December 2009. Dr. Harrington's role is solely administrative, as Director of the Cardiovascular Clinical Trials. ———————, currently approved for the treatment of hypertension, is one of the many competing products to Avalide.

Further, Dr. Harrington is Co-Director, Cardiovascular Research, and Director, Cardiovascular Clinical Trials, Duke Clinical Research Institute (DCRI). The DCRI's Cardiovascular Clinical Trials unit has received research funding from the sponsors of ———, as well as from ———, ———————, ———, ———, and ———————, firms that make competing products. These funds are for clinical trials of products unrelated to Avalide and its competitors. For all but three of these trials, Dr. Harrington's involvement is solely administrative as Director of Cardiovascular Clinical Trials. Dr. Harrington is involved, either as an investigator or steering committee member, in three trials sponsored by ———————, ———————, and ——— ———————. For these three studies, a portion of the funds offset his salary. Dr. Harrington's employer's interests in these firms are unrelated to the issue to be discussed and the competing products. Arguably, these interest do not constitute financial interests 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 member of the Cardiovascular and Renal Drugs Advisory Committee, Dr. Harrington potentially could become involved in matters that could affect his and his employer's 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 waiver permitting Dr. Harrington 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. Harrington that would allow him to participate fully in the matter previously described.

First, with respect to Dr. Harrington's consulting, it is important to note that his past consults were unrelated to Avalide and its competing products and that he has no consulting currently planned.

Second, the consulting fees anticipated are minimal and will be donated to educational charities.

Third, with respect to the DCRI's participation in study of ———————, although Dr. Harrington's employer has a financial interest in ———, he himself has no financial interest in either the drug or the company. Although the financial interests of an employer impute to the individual under 18 U.S.C. §208, 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.

Fourth, although the funding from ——— is substantial, it does not constitute a significant portion of the Institute's total research funding. The Duke Clinical Research Institute is one of the world's largest academic clinical research organizations with an annual budget of over $——————— dollars. With over 920 faculty and staff, the DCRI is capable of providing a full range of research services and scientific leadership in the conduct of clinical research in more than twenty therapeutic areas.

In addition, ———, ———————, ———, **and** ——————— are very large, well-established companies. Thus, the recommendations of the Committee would not be expected to impact the stability of these firms.

Further, the uniqueness of Dr. Harrington's qualification justifies granting this waiver. The upcoming meeting is intended to explore with the Advisory Committee a novel basis for the approval for first-line use of combination antihypertensive drug products. Dr. Harrington is a cardiologist with a great deal of clinical trial experience and more than 150 peer-reviewed research publications. As head of the Duke Clinical Research Institute, Dr. Harington has unique experience in the design and implementation of a broad spectrum of cardiovascular clinical trials. In addition, he helps lead that institution's efforts to apply the lessons of clinical trials to clinical practice within the Duke and Durham community, and, though his involvement on the Cardiovascular Research Committee of the American College of Cardiology, to the nation at large. At past advisory committee meetings, Dr. Harrington has distinguished himself as a major contributor in synthesizing available information and formulating a logical basis for

regulatory decision-making. I therefore believe his contributions to the upcoming meeting to be of high importance.

Moreover, the standing core CRDAC committee was instrumental in providing significant guidance and recommendations to the Agency during a 2006 Advisory Committee discussing important considerations for labeling changes for hypertensive drugs. The discussions surrounding this topic of discussion are germane to regulatory decisions that will affect the broader class of combination hypertensive products. Thus what is key is that those previously involved in these discussions are able to weigh in and provide the continuity needed for this meeting. Thus no additional non-member SGEs have been given consideration with respect to participation in this meeting.

Lastly, 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. The uniqueness of Dr. Harrington's qualifications justifies granting this waiver. At this meeting, the Committee will explore a novel basis for the approval for first-line use of combination antihypertensive drug products. Dr. Harrington is a Director of Duke's Clinical Research Institute (DCRI). Dr. Harrington has unique experience in the design and implementation of a broad spectrum of cardiovascular clinical trials. In addition, he helps lead the DCRI's efforts to apply the lessons of clinical trials to clinical practice within the Duke and Durham community, and, though his involvement on the Cardiovascular Research Committee of the American College of Cardiology, to the nation at large. His main research interests are cardiovascular disease, interventional cardiology, acute ischemic disease, cardiovascular clinical trials, and evidence based medicine. Dr. Harrington is actively involved in studying the mechanism of disease of the acute coronary syndromes, in understanding the issues of risk stratification in the care of patients with acute ischemic coronary syndromes and in trying to better understand and improve upon the methodology of large clinical trials. As a cardiologist and researcher, Dr. Harrington has an enormous

amount of clinical trial experience and has participated in all phases of a clinical trial's operations, from protocol development and approval, recruitment of sites and patients, enrollment issues, coordination of activities with sponsors, presentation of results and manuscript publication as well as the FDA drug approval process. At past Committee meetings, Dr. Harrington has distinguished himself as a major contributor in synthesizing available information and formulating a logical basis for regulatory decision-making. Therefore, the Center believes Dr. Harrington's contribution to be of high importance.

Accordingly, I recommend that you grant Robert Harrington, M.D., a waiver that will permit him to participate in all official matters concerning Supplemental New Drug Application (NDA) 20-758/S-037, Avalide (irbesartan/HCTZ), sponsored by Bristol Myers Squibb and Sanofi-Synthelabo, a subsidiary of Sanofi-Aventis, for use in the treatment of hypertension in patients unlikely to achieve blood pressure goals on one drug. I believe that such a waiver is appropriate because in this case, the need for the services of Dr. Harrington outweighs the potential for a conflict of interest created by the financial interests attributable to him.

CONCURRENCE: /S/ 3/23/07

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/ 3/26/07

Randall Lutter, Ph.D.
Associate Commissioner for Policy
and Planning

Date