DEPARTMENT OF HEALTH & HUMAN SERVICES

MEMORANDUM

Food and Drug Administration
Rockville MD 20857

DATE: November 14, 2005

TO: Shelia Dearybury Walcoff, Esq.
Associate Commissioner for External Relations
Food and Drug Administration

THROUGH: Jenny Slaughter
Director, Ethics and Integrity Staff
Office of Management Programs
Office of Management

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

SUBJECT: Conflict of Interest Waiver for Brian Gage, M.D.

I am writing to request a waiver for Brian Gage, M.D., a consultant to the Center for Drug Evaluation and Research, from the conflict of interest prohibitions of 18 U.S.C. §208(a). The appointing official may grant waivers under 18 U.S.C. §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. Gage a 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. Since Dr. Gage 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 functions of the Pharmaceutical Science Advisory Committee, as stated in its Charter, are to provide advice on scientific and technical issues concerning the safety, and effectiveness of human generic drug products for use in the treatment of a broad spectrum of human diseases, and as

required, any other product for which the Food and Drug Administration has regulatory responsibility, and make appropriate recommendations to the Commissioner of Food and Drugs. The Committee may also review Agency sponsored intramural and extramural biomedical research programs in support of FDA's generic drug regulatory responsibilities.

Dr. Gage has been asked to give a presentation on "New Insights on Warfarin: How CYP 2C9 and VKORC1 Information May Improve Benefit/Risk," and answer questions related to his presentation at the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science. The Subcommittee will discuss current evidence related to the pharmacogenetics of warfarin as a potential basis for label updates.

Dr. Gage has advised the Food and Drug Administration (FDA) that he has financial interests that could potentially be affected by his participation in the matter described above. Dr. Gage is a consultant for [redacted] on unrelated issues. [redacted] is the sponsor of [redacted], a competing product to warfarin.

Dr. Gage is the PI leading a team from the Washington University School of Medicine, currently involved in grant from the National Heart, Lung and Blood Institute (NHLBI) to determine how clinical and genetic factors predict a patient's response to therapy. Based on a 400 patient, pilot study, they will use the data to refine and validate an algorithm developed for determining the right dose of blood thinner warfarin.

He will also be a co-investigator (though PI at his institution) on a study funded by the National Human Genome Research Institute (NHGRI) on Genetic Factors Influencing Warfarin Dose. The study will begin January 1, 2006 and is projected to end December 31, 2010.

Potential label updates with regards to the pharmacogenetics of Warfarin is the issue before the Clinical Pharmacology Subcommittee.

As a consultant presenting to the Clinical Pharmacology Subcommittee, Dr. Gage could potentially become involved in matters that could affect his and his employer's financial interests. Under section 208, 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. Gage 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 limited waiver to Dr. Gage that would allow him to make a presentation to the committee regarding "New Insights on Warfarin: How CYP 2C9 and VKORC1 Information May Improve Benefit/Risk," and answer questions related to his presentation. Under the terms of this limited waiver, Dr. Gage will not participate in the committee's discussions, deliberations, or voting.

First, it is important to consider that Dr. Gage's conflict is mitigated by the fact that FDA has decided to limit his participation. Given the need for his expertise, Dr. Gage will give a presentation to the subcommittee and answer questions directly related to his presentation. He will not be allowed to participate in any of the committee's discussions, deliberations, or voting with respect to the current evidence related to the pharmacogenetics of warfarin as a potential basis for label updates.

Although the study that Dr. Gage is involved in and the upcoming study are related to the issue before the committee, it is important to note that neither of these studies are funded by the manufacturers or any other commercial entity, but rather they are funded by institutes of the National Institutes of Health. The fact that the source of funding is a federal agency, rather than a commercial entity, minimizes the likelihood or appearance that Dr. Gage is subject to influence by the manufacturers of warfarin or their competitor's. Thus, the potential for an actual or apparent conflict of interest is minimal.

Dr. Gage's consulting for [redacted] is unrelated to the particular matter in which he is being asked to participate, or to the competing products. Arguably, his interest does not constitute a financial interest in the particular matter within the meaning of 18 U.S.C. §208(a); nevertheless, in the utmost of caution, I recommend that this waiver be granted.

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 various advisory committee members and Dr. Gage's participation will contribute to the balance of views represented and the diversity of opinions and expertise. 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. Gage is Associate Professor, Medicine, Division of General Medical Sciences; Medical Director, Barnes-Jewish Hospital Blood Thinner Clinic; Medical Director, Barnes-Jewish Hospital and Washington University Physicians Network Anticoagulation Service, Washington University School of Medicine. Dr. Gage's area of expertise is in clinical research of anti-coagulation, antithrombotic therapy, deep vein thrombosis, and blood thinners, aspirin, warfarin, coumadin and stroke prevention. He has written numerous peer-reviewed journal articles and manuscripts in these areas. In addition, he is a member of several professional societies and organizations including, the American College of Physicians, the American Heart Association Scientific Counsel on Stroke, and the Anticoagulation Forum. I believe Dr. Gage's presentation will provide the committee with much needed information on the pharmacogenetics of warfarin and is essential for an appropriate discussion of the topic to be considered at this meeting.

Accordingly, I recommend that you grant Brian Gage, M.D., a limited waiver that would allow him to give a presentation on "New Insights on Warfarin: How CYP 2C9 and VKORC1 Information May Improve Benefit/Risk," and answer questions related to his presentation. Under the terms of this

Acknowledgement and Consent for Disclosure of A Limited Waiver Under 18 U.S.C. §208(b)(3)

To: Cindi Abernethy, Public Health Analyst, FDA/CDER/Advisor
Fax: 301-827-6801
From: Brian Gage, M.D.

Committee: Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science

Meeting Date: November 14, 2005

I acknowledge that contingent upon public disclosure of the financial interests listed below, I am eligible to receive a limited waiver under 18 U.S.C. §208(b)(3). Under the terms of the limited waiver, I will be permitted to give a presentation on "New Insights on Warfarin: How CYP 2C9 and VKORC1 Information May Improve Benefit/Risk," and answer questions directly related to my presentation. I will be excluded from participating in the committee's discussions, deliberations, or voting related to the current evidence related to the pharmacogenetics of warfarin as a potential basis for label updates.

Type and Nature of the Interest

Type of Interest	Nature	Magnitude
Unrelated Consulting	Sponsor of a competing product.	Less than $10,001 per year.
Related Grant	Federally Funded	Greater than $300,000 per year.
Related Grant	Federally Funded	Less than $100,000 per year.

I hereby request that FDA make this information publicly available on my behalf at the start of the advisory committee meeting for which it is issued. The public disclosure will be accomplished by reading the statement into the record and by making a written copy publicly available at the time of the meeting. I understand that without public disclosure of the interests, the limited waiver is not valid.

B Gage
Signature of SGE

11/7/05
Date