DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

MEMORANDUM

DATE: September 13, 2006

TO: Randall Lutter, Ph.D.
Associate Commissioner for
Policy and Planning
Food and Drug Administration

THROUGH: Jenny Slaughter
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 Jaap W. Mandema, Ph.D.

I am writing to request a waiver for Jaap W. Mandema, Ph.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 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. Mandema 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. Mandema 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. Mandema has been asked to participate in the Clinical Pharmacology Subcommittee, of the Advisory Committee for Pharmaceutical Science, meeting where the subcommittee will discuss the impact of using prior knowledge on drug development and regulatory decisions. Prior knowledge of disease change over time and covariates, placebo variation, and drug effects can be used to make better decisions and design more informative clinical trials. The issue under discussion is a particular matter of general applicability. Particular matters of general applicability focus on a discrete and identifiable class of persons (i.e., all pharmaceutical firms) but do not involve specific parties (i.e., a specific firm's product).

The function of the Advisory Committee for Pharmaceutical Science, as stated in its charter, is 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. Mandema has advised the Food and Drug Administration that he, ———, and employer have financial interests that could potentially be affected by his participation in the issue under discussion. Dr. Mandema is President and CEO of Quantitative Solutions, Inc., a consulting firm that provides modeling and simulation solutions to the pharmaceutical industry. Quantitative Solutions currently has consulting contracts with ———, ———, ——— ———, ———, ———, and ———. The consulting for these companies concerns all products.

In addition, Quantitative Solutions has consulting contracts with ———, ———, and ——— concerning cardiovascular products.

Quantitative Solutions also has consulting contracts with ——— and ——— regarding dialysis products; ——— ——— regarding epilepsy drugs; ——— regarding diabetes products; ——— regarding epilepsy/analgesia products; and ——— regarding Parkinson's products.

Dr. Mandema is either the Principal Investigator or co-Investigator for these projects. The funding goes directly to Quantitative Solutions, not to him. He is an employee of Quantitative Solutions. It is impossible for him to determine what fraction of the remuneration for each of these consulting contracts flows to him in the form of salary, bonus, and dividend payments.

In addition, Dr. Mandema owns stock in ———, ———, and ——— . ——— owns stock in ——— and ———. The stocks represent a small percentage of their total net worth.

Dr. Mandema is a director of the Mandema Family Foundation, a charitable foundation. The Foundation currently contains stock in ———, ———, ———, and ——— ———. He is also a director of a Charitable Unit Remainder Trust (CRUT). The CRUT contains stock in ———, ———, ———, and ———.

As a consultant advising the Clinical Pharmacology Subcommittee of the Advisory Committee for Pharmaceutical Science, Dr. Mandema potentially could become involved in matters that could affect his personal and imputed 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. Mandema 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. Mandema, which would permit him to participate in the subcommittee's discussion of the impact of using prior knowledge on drug development and regulatory decisions.

First, this waiver is justified, in part, because of the general nature of particular matters of general applicability.

It is well recognized that particular matters of general applicability pose far less risk of a conflict of interest. Particular matters of general applicability include regulations, points-to-consider, guidelines, and policies governing classes of individuals, products, and organizations. Particular matters of general applicability do not include particular matters involving specific parties, such as recommendations regarding a specific product, or enforcement matters involving known parties. Dr. Mandema's participation in the particular matter of general applicability under discussion will not have a special or distinct impact on any of his personal and imputed financial interests, other than as part of a class.

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. Mandema's participation will contribute to the balance of views represented and the diversity of opinions and expertise. The subcommittee'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. Jaap W. Mandema, Ph.D., is President and CEO of Quantitative Solutions, Inc., a consulting firm that provides modeling and simulation solutions to the pharmaceutical industry. Previously, Dr. Mandema was Chief Scientific Officer of Extropy Pharmaceuticals, a startup company focused on developing drugs to treat children's illnesses. Prior to joining Extropy, he was Senior Vice President and Chief Scientific Officer at Pharsight, a company that provides software and consulting services to the pharmaceutical industry to improve the efficiency of drug development. Dr. Mandema has also been Director of New Products Discovery at ALZA Corporation. Dr. Mandema started his career as an Assistant Professor of Pharmaceutical Sciences at the Department of Anesthesia, Stanford University School of Medicine, where he led a lab researching the pharmacodynamic interactions among analgesic and anesthetic drugs. Dr. Mandema's research interests are in the application of modeling and simulation to optimize treatment strategies, trial designs, and drug development decision-making. In 2005, Dr. Mandema was

selected by the American Society for Clinical Pharmacology and Therapeutics to receive a Leon I. Goldberg Young Investigator

Award. Dr. Mandema's vast experience in drug development is essential to the subcommittee's discussions and will help provide a foundation for developing advice and recommendations that are fair and comprehensive.

Accordingly, I recommend that you grant Jaap W. Mandema, Ph.D., a waiver that will permit him to participate in the Clinical Pharmacology Subcommittee, of the Advisory Committee for Pharmaceutical Science, meeting where the subcommittee will consider the impact of using prior knowledge on drug development and regulatory decisions. I believe that such a waiver is appropriate because in this case, the need for the services of Dr. Mandema outweighs the potential for a conflict of interest created by the financial interests attributable to him.

CONCURRENCE: /s/ 9/22/06

Jenny Slaughter
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/ 9/25/06

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

Date