DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

DATE: October 25, 2007

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 Ralph D'Agostino, Ph.D.

I am writing to request a waiver for Ralph D'Agostino, Ph.D., a member of the Nonprescription 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. D'Agostino a 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. D'Agostino 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 Nonprescription Drugs Advisory Committee is to review and evaluate available data concerning the safety and effectiveness of over-the-counter (nonprescription) human drug products, or any other FDA-regulated product, for use in the treatment of a broad spectrum of human symptoms and diseases and advise the Commissioner either on the promulgation of monographs establishing conditions under which these drugs are generally recognized as safe and effective and not misbranded or on the approval of new drug application for such drugs. The Committee also serves as a forum for the exchange of views regarding the prescription and nonprescription status, including switches from one status to another, of these various drug products and combinations thereof.

Dr. D'Agostino has been asked to participate in the December 14, 2007, meeting concerning the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as Over-The-Counter (OTC) oral nasal decongestants. The discussion at the meeting will address a citizen petition submitted to FDA February 1, 2007 (Docket No. 2007P-0047; CP1), which asserts that the available data do not support the adult and pediatric doses of phenylephrine hydrochloride and phenylephrine bitartrate that are generally recognized as safe and effective in the OTC drug monograph for Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products (the Cough – Cold monograph) in 21 CFR Part 341. The meeting will focus on review of existing safety and efficacy data and the petitioner's request that the Cough-Cold monograph be amended to increase the adult dose of phenylephrine hydrochloride from 10 to 25 milligrams (mg) and of phenylephrine bitartrate from 15.6 to 40 mg.

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

Dr. D'Agostino has advised the Food and Drug Administration (FDA) that he has a financial interest that could potentially be affected by his participation in the matter described above. Dr. D'Agostino is on a Data Safety Monitoring Board (DSMB) for ——— on an unrelated issue. ——— is a firm that could potentially be affected by the committee's discussions and recommendations. ——— makes over-the-counter (OTC) products that contain phenylephrine hydrochloride.

As a member of the Nonprescription Drugs Advisory Committee, Dr. D'Agostino could become involved in matters that could affect his financial interests. Under section 712(c)(2)(B), 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 waiver permitting Dr. D'Agostino to participate in such matters if necessary to afford this committee essential expertise.

For the following reasons, I believe that it would be appropriate for you to grant a waiver to Dr. Ralph D'Agostino that would allow him to participate in the matter described because his voting participation is necessary to afford the committee essential expertise.

First, it is important to consider that Dr. D'Agostino's interest in ——— is unrelated to the products and issues coming before the committee.

Second, Dr. D'Agostino's financial interest in [redacted] is not so substantial as to preclude his participation in this meeting. He receives minimal compensation for serving on the Data Safety Monitoring Board.

Third, committee decisions are not expected to affect the viability of [redacted]. [redacted]. The sales of its OTC products that contain phenylephrine hydrochloride or phenylephrine bitartrate account for only a fraction of [redacted] total sales revenue.

Fourth, there are more than five affected products on the market for the treatment of nasal congestion.

Fifth, according to the Division of Nonprescription Clinical Evaluation, the uniqueness of Dr. D'Agostino's qualifications justifies granting this waiver. Dr. D'Agostino received his doctorate in Mathematical Statistics from Harvard University. He has an outstanding record of research and publications in biostatistics. He has received numerous honors for his work including the Commissioner's Special Citation from the FDA, twice. Dr. D'Agostino has received numerous federal grants supporting his work. He presently serves as a consultant to the Divisions of Biometrics, Oncology, and to the Office of Non-Prescription Products at the FDA, and he has previously served as a member of advisory committees including the Nonprescription Drugs Advisory Committee (NDAC) from 1995-1998, and the Gastrointestinal (GI) Advisory Committee from 1990-1994. He also participated on the committee that recently (2006) discussed issues regarding consumer studies such as label comprehension and actual use studies that are instrumental to approval of OTC products. His ability to analyze statistical problems and present concise interpretation to non-statistical advisory committee members has been and continues to be invaluable.

Due to his previous experience on the Nonprescription Advisory Committee, Dr. D'Agostino understands the complex regulatory scheme by which OTC drug products are marketed and the data that is required to amend any existing monographs. With his extensive experience in reviewing clinical trial data, Dr. D'Agostino is able to discuss clinical issues as they relate to statistical certainty. For this meeting, one of the most important issue for discussion is whether clinical studies reported in the medical literature, and reviewed by the Advisory Panel for cough and cold products, constitute a sufficient basis for continued marketing of the decongestant phenylephrine. Dr. D'Agostino will be able to opine on the quality and validity of these studies and the two related meta-analyses. Both of these meta-analyses involve complex statistical assessments, reaching different conclusions, and Dr. D'Agostino's expertise is needed to explain the differences between the two statistical methods used and interpret the contradictory findings. Due to Dr. D'Agostino's unique combination of experience in matters where epidemiologic surveillance and complex statistical analysis are required, his in-depth knowledge of nonprescription drug products, and his experience with the advisory committee process, the review Division was unable to locate another similarly qualified biostatistician to serve in his stead.

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. D'Agostino is the Executive Director of Biostatistics at the Harvard Clinical Research Institute (HCRI). He is an internationally recognized expert in the areas of longitudinal data analysis, multivariate data analysis, biostatistics and robust procedures. He is also a professor of mathematics, statistics, and public health at Boston University, and is an expert in statistical evaluations of data. Dr. D'Agostino is a member of the American Statistical Association and the Cardiovascular Epidemiology section of the American Heart Association. He is a co-author of four books on Factor Analysis, Goodness-of-Fit Techniques, Mathematical Models in Health Service Research, and Engineering Statistics, and has served on the editorial board of the journal of the American Statistical Association, Biostatistics, and Statistics in Medicine. I believe that Dr. D'Agostino's broad clinical and research experience will contribute to the diversity of opinions and expertise represented on the committee.

Accordingly, I recommend that you grant Ralph D'Agostino, Ph.D., a waiver that would allow his voting participation in all official matters concerning the safety and effectiveness of phenylephrine hydrochloride and phenylephrine bitartrate as Over-The-Counter (OTC) oral nasal decongestants. The meeting will focus on review of existing safety and efficacy data and the petitioner's request that the Cough-Cold monograph be amended to increase the adult dose of phenylephrine hydrochloride from 10 to 25 milligrams (mg) and of phenylephrine bitartrate from 15.6 to 40 mg. I believe that such a waiver is appropriate because in this case, Dr. D'Agostino's voting participation is necessary to afford the committee essential expertise.

DECISION:

_X_ Waiver granted based on my determination, made in accordance with section 712(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act, that voting participation is necessary to afford the committee essential expertise.

____ Waiver granted based on my determination, made in accordance with section 712(c)(2)(B) of the Federal Food, Drug, and Cosmetic Act, that nonvoting participation is necessary to afford the committee essential expertise.

_____ Waiver denied.

/s/ 11/19/07

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