

investigational human drug products for use in the practice of psychiatry and related fields and make appropriate recommendations to the Commissioner of Food and Drugs.

Dr. Leon has been asked to participate in all official matters concerning new drug application (NDA) 22-173 Zyprexa Adhera (olanzapine pamoate depot) long acting intramuscular (IM) injection 210mg, 300mg, and 405 mg per/vial, sponsored by Eli Lilly & Company, for treatment of schizophrenia. A particular safety concern for discussion is the occurrence of severe somnolence in some patients who are administered this depot formulation of olanzapine.

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

Dr. Leon has advised the Food and Drug Administration (FDA) that he has a current financial interest which could potentially be affected by his participation in the matter described above. **Dr. Leon serves on _____'s Data Safety Monitoring Board (DSMB) for _____, and was recently recruited by _____ to serve on their DSMB for _____. _____ and _____ are competing products to Zyprexa Adhera, the product coming before the committee. Dr. Leon also serves on _____'s DSMB for _____, an obesity drug. This drug is unrelated to Zyprexa Adhera.**

In addition, Dr. Leon has served on _____'s DSMB for _____ in the past. Arguably, his past interest does not constitute a financial interest in the particular matter under section 208(a) since these interests are unrelated to the issue at hand. Nevertheless, in the utmost of caution, I recommend that this waiver be granted.

As a Temporary Voting Member of the Psychopharmacologic Drugs Advisory Committee, Dr. Leon potentially could become involved in matters that could affect his financial interest. Under section 208, he is prohibited from participating in such matters. However, as noted above, you have the authority under section 208(b)(3) to grant a waiver permitting Dr. Leon 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. Leon that would allow him to participate fully in the matter described because the need for his services greatly outweighs the conflict of interest created by this financial interest.

First, although Dr. Leon serves on Data Safety Monitoring Boards (DSMBs) for _____ and _____, it is important to consider the main purpose of a DSMB. A Data Safety Monitoring Board is an independent group of experts who monitor patient safety and treatment efficacy data while a clinical trial is ongoing. It is a separate entity that conducts an independent, objective review of all accumulated data from both blinded and un-blinded clinical trials in such a manner as to maximize benefit to the trial participants and to the research effort. The primary mandate of the DSMB is to protect patient safety. Participants in the review of masked or confidential data and discussions regarding continuance or stoppage of the study should have no conflict of interest with or financial stake in the research outcome. And in this case, Dr. Leon does not have any financial stake in the competing product or firm. In addition, Dr. Leon's involvement with _____'s DSMB is unrelated to the matter coming before the committee.

Second, this interest is not so substantial as to preclude Dr. Leon's participation. Dr. Leon receives moderate compensation from _____ and _____; and minimal compensation from _____ for serving on DSMBs.

Third, according to the Review Division, the uniqueness of Dr. Leon's qualification justifies granting this waiver. Not only is Dr. Leon the only biostatistician participating in the Psychopharmacologic Drugs Advisory Committee meeting, but he is a biostatistician with expertise in psychiatric drugs which makes him even more vital for the required analysis of clinical trial data in this meeting. The meeting will examine the safety and efficacy of the parenteral treatment of schizophrenia with olanzapine long-acting injection. In order to have a balanced discussion of clinical trial design, a biostatistician is critical to provide input regarding time to onset of adverse drug reactions, clinical endpoints and related deltas, powering of studies, as well as comparator arms and treatment durations. Dr. Leon's vast research experience and knowledge of clinical trial design, adverse drug reactions in clinical trials, and protocol development as a statistician makes him uniquely qualified to participate and will allow a quantitative perspective in the determination of the overall risk and benefit assessment. I believe that participation by Dr. Leon in the committee's deliberations will contribute to the diversity of opinions and expertise represented on the committee.

Lastly, locating qualified individuals without disqualifying financial interest to serve on this advisory committee has been very difficult. The Division of Psychiatry Products (DPP) contacted 2 experts but was unable to locate a less conflicted biostatistician with Dr. Leon's level of expertise in clinical psychiatric research. The Division's experience with Dr. Leon has been unmatched. Dr. Leon's participation in previous Psychopharmacologic Drugs Advisory Committee (PDAC) makes him an invaluable resource to FDA for this meeting. Dr. Leon is both qualified and experienced to guide and advise the clinicians on PDAC as to the most scientifically valid interpretation of the studies at matter. Due to his previous experience on the PDAC, Dr. Leon understands the complex regulatory scheme by which clinical trial data is reviewed and interpreted and how this is utilized to support the NDA at hand. Dr. Leon's unique combination of delivering this guidance in the most qualified manner to provide balance in approach and ensure a sound scientific discussion and his experience with the advisory committee process makes him uniquely qualified. If Dr. Leon is recused, it will leave insufficient biostatistical expertise on the panel to adequately address the meeting issues. To that end, the Division requests that a waiver be granted for Dr. Andrew Leon to participate as there has been a genuine effort to secure individual participation and representation with minimal conflict of interest.

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. Leon is the Director of the Methods Core for the Weill Cornell Advanced Center for Interventions and Services Research in Late Life Depression. He is currently involved in an ongoing National Institute of Health-funded research project, "Dynamic Techniques for Treatment Effectiveness Analyses" (R01 MH0640447) since Year 2001. He collaborates in numerous clinical

trials and epidemiologic studies. He was also awarded the National Institute of Mental Health, New Clinical Drug Evaluation Unit (NCDEU) New Investigators' Award in Year 1992.

Accordingly, I recommend that you grant Andrew Leon, Ph.D., a waiver that would allow him to participate in all official matters concerning new drug application (NDA) 22-173 Zyprexa Adhera (olanzapine pamoate depot) long acting intramuscular (IM) injection 210mg, 300mg, and 405 mg per/vial, sponsored by Eli Lilly & Company, for treatment of schizophrenia. I believe that such a waiver is appropriate because in this case, the need for the services of Dr. Leon outweighs the potential for a conflict of interest created by the financial interest attributed to him.

DECISION:

Waiver granted based on my determination, made in accordance with section 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.

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

1/14/08
Date