



Waiver to Allow Participation in a Food and Drug Administration Advisory Committee

DATE: April 22, 2009

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/
Director, Advisory Committee Oversight and Management Staff
Office of Policy, Planning, and Preparedness

FROM: Jayne E. Peterson _____ /S/
Director
Division of Advisory Committee and Consultant Management
Center for Drug Evaluation and Research

Name of Temporary Voting Member: Richard Malone, M.D.

Committee: Psychopharmacologic Drugs

Meeting date: June 9 - 10, 2009

Description of the Facts on Which the Waiver is Based:

Type, Nature, and Magnitude of the Financial Interest(s):

Dr. Malone's employer, Drexel University, was awarded a research contract from the National Institutes of Mental Health (NIMH) to study Zyprexa (olanzapine) for the treatment in children with autism. The funding is provided by NIMH and the study drug is provided by Eli Lilly.

Dr. Malone was negotiating a contract with NIMH for the study of (b) (4) in autism, but has since learned that the contract will not be funded. Dr. Malone plans to re-submit a similar contract to NIMH in May and June 2009.

If awarded, funding would be provided by NIMH, and the study drug and placebo would be asked to be provided by (b) (4)

Lastly, a letter of intent has been submitted to the Department of Defense (DOD), to submit a grant proposal in June 2009 regarding (b) (4) for the study of autism. If awarded, funding would be provided by DOD and (b) (4) would be asked to provide the study drug and placebo.

(b) (4) All of these studies are for the treatment of autism, an indication unrelated to the issues coming before the committee. Dr. Malone is/will be the Principal Investigator at the University for these studies.

The magnitude of the interests are between \$50,001 - \$100,000 per year for the Zyprexa study; \$100,001 - 300,000 each, per year for the pending NIMH and Department of Defense (b) (4) studies;

Description of the Particular Matter to Which the Waiver Applies:

On June 9-10, 2009, the committee will discuss safety and efficacy issues for the following new drug applications (NDAs): 1) NDA 20-639/S-045 and S-046: Seroquel (quetiapine fumarate), AstraZeneca Pharmaceuticals LP, for (a) the acute treatment of schizophrenia in adolescents (13-17 years of age), and (b) the acute treatment of bipolar mania in children (10-12 years of age) and adolescents (13-17 years of age); 2) NDA 20-825/S-032: Geodon (ziprasidone hydrochloride), Pfizer Inc., for the acute treatment of manic or mixed episodes associated with bipolar disorder, with or without psychotic features in children and adolescents ages 10-17 years; and 3) NDA 20-592/S-040 and S-041: Zyprexa (olanzapine), Eli Lilly and Company, for (a) the acute treatment of manic or mixed episodes associated with bipolar I disorder, and (b) the acute treatment of schizophrenia in adolescents. The committee will be asked to vote on whether or not these products have been shown to be effective and acceptably safe for these pediatric indications.

Additional Facts: none

Basis for Granting the Waiver:

First, it is important to consider that the studies that Dr. Malone's employer, Drexel University, is involved in or negotiating for, with respect to (b) (4) and Zyprexa are for an unrelated indication than what is coming before the committee.

Even if the committee recommends that the supplemental applications not be approved, it is unlikely to affect NIMH, (b) (4) Eli Lilly or the Department of Defense's (DOD) willingness to continue or approve grants to study these products in different indications. These products are established on the market for other indications and have been for several years. (b) (4) has been on the market since (b) (4), and is approved for use in (b) (4) patients. Zyprexa (olanzapine) has been on the market since 1996, and is approved for use in schizophrenia, as well as manic or mixed episodes associated with Bipolar I Disorder.

Furthermore, any positive or adverse recommendations concerning (b) (4) or Zyprexa, or subsequent actions by the Agency, are unlikely to affect the economic stability of (b) (4) or Eli Lilly or the likelihood that NIMH or DOD will provide funding to the research. Eli Lilly is one of the pharmaceutical industry leaders with products marketed in 143 countries and clinical research conducted in more than 50 countries. In 2008, total product sales increased 9 percent and topped \$20 billion with 8 products each exceeding \$1 billion. (b) (4) is the (b) (4) research-based biomedical and pharmaceutical company. In 2008, (b) (4) earned \$ (b) (4) in revenues and invested \$ (b) (4) in research and development. It is unlikely that the committee's recommendations concerning Eli Lilly's Zyprexa (olanzapine) and (b) (4) will significantly impact the economic stability of these companies.

In addition, NIMH is one of 27 institutes in the National Institutes of Health. As part of the NIMH mission, they generate research and promote research training. NIMH funds research across the country as well as in NIMH studies in the internal research program. Through its extramural program, NIMH supports more than 2,000 research grants and contracts at universities and other institutions across the country and overseas. The United States Department of Defense (DOD) is the federal department charged with coordinating and supervising all agencies and functions of the government relating directly to national security and the military. With estimated annual funding of \$786 billion for fiscal year 2009, the Defense Appropriations Act also provides \$8 million to the Department of Defense Autism Research Program (ARP) to find and fund the best research to improve the lives of individuals with autism spectrum disorders. This program is administered by the US Army Medical Research and Materiel Command through the Office of the Congressionally Directed Medical Research Programs (CDMRP).

It is unlikely that any action, short of a "clinical hold" determination, would have an impact on Dr. Malone's employer's studies in autism, an unrelated indication to the issues coming before the committee. Drexel University is a private coeducational university ranked consistently among the "Best National Universities-Top Schools" by U.S. News & World Report in its annual "America's Best Colleges". Per the September 23, 2008 financial report, Drexel University reported total net assets of \$1.47 million, and \$627 thousand of total operating revenue.

Dr. Richard Malone is uniquely qualified to discuss the issues as he has expertise in two areas of concern for us at this meeting: Child Psychiatry and Child Psychopharmacology. He is a Professor of Psychiatry and Professor of Pharmacology and Physiology at Drexel University College of Medicine. Dr. Malone holds several board certifications, including Child and Adolescent Psychiatry. He is actively involved in multiple extra-mural scientific review committees with the National Institute of Mental Health and the American Academy of Child and Adolescent Psychiatry. He served as a member of the Psychopharmacologic Drugs Advisory Committee (PDAC) from 2000 to 2004, and has served as an SGE consultant from 2004 until the present. At past advisory committee meetings, Dr. Malone has distinguished himself as a major contributor in synthesizing available information and formulating a logical basis for regulatory decision-making. He has demonstrated efficiency in preparing thoroughly and guiding critical topics of discussion with challenging insights and perceptive inquiries. His ability to articulate important information facilitates an enhanced, well-balanced discussion amongst the

Committee members. In addition, Dr. Malone's expertise in complex clinical trials will contribute to the committee discussions on the NDAs under consideration.

Dr. Malone's expertise in Child Psychiatry and Child Psychopharmacology is essential to a complete understanding of the need for treatment in the pediatric population. Of the 23 psychiatrists invited for this meeting, fifteen are Child Psychiatrists; however, Dr. Malone is the only invitee with expertise in Child Psychopharmacology as well. Drugs behave differently in adults than they do in pediatric patients, and pediatric patients respond differently to different doses of drug; an understanding of child psychopharmacology is essential to understanding these differences taking into account both the developing systems of younger children as well as the maturing systems of adolescents. Dr. Malone's expertise not only in pharmacology, but specifically Child Psychopharmacology which deals with those drugs which are used to treat psychiatric diseases in children uniquely enable Dr. Malone to address these areas of discussion during the meeting. While CDER has a few experts as consultants in the area of Psychopharmacology, Dr. Malone is the sole expert in psychopharmacology with a specific focus on Child Psychopharmacology. Taken into account his experience with advisory committees and in particular, his experience with the PDAC, he was the only person invited to this meeting. The division has been able to rely on Dr. Malone in the past for these very reasons and the division is requesting that he be allowed to participate at this meeting. Given the gravity of the safety issues and the importance in discussing all appropriate areas involving children, the division believes Dr. Malone's contribution to the Agency's consideration of these applications will far outweigh any conflict of interest that might be perceived. The division urges in the strongest possible terms that Dr. Malone be permitted to attend and fully participate in the June 9-10, 2009 PDAC meeting.

As described above, we believe that the interest of the Government in Dr. Malone's participation outweighs the concern that a reasonable person may question the integrity of the Agency's programs and operations.

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Thus we are requesting a waiver for Richard Malone, M.D., a temporary voting member of the Psychopharmacologic Drugs Advisory Committee, from the conflict of interest prohibitions of 18 U.S.C. §208(a).

Certification:

 X The individual may participate – The need for the Special Government Employee’s services outweighs the potential for a conflict of interest.

 X The individual may participate – The individual’s participation is necessary to afford the advisory committee essential expertise.

Limitations on the Regular Government Employee’s or Special Government Employee’s Ability to Act:

 Non-voting

 Other (specify):

 Denied – The individual may not participate.

 /S/
Randall W. Lutter, Ph.D.
Deputy Commissioner for Policy

 5/21/09
Date