DATE: October 30, 2024

TO: Walter S. Dunn, M.D., PhD
Member, Psychopharmacologic Drugs Advisory Committee
Center for Drug Evaluation and Research
Food and Drug Administration

FROM: Robert M. Califf, M.D.
Commissioner of Food and Drugs
Food and Drug Administration

SUBJECT: Waiver to Allow Participation in a Food and Drug Administration Advisory Committee Meeting, under Title 18, Section 208(b)(l) of the United States Code

LEGAL AUTHORITY

The criminal conflict of interest statute, 18 U.S.C. § 208(a), prohibits a federal executive branch employee from participating personally and substantially in any particular matter that will have a direct and predictable effect on the employee's financial interests or on the financial interests of certain other persons whose financial interests are imputed to the employee. Under 18 U.S.C. § 208(b)(l), however, the employee's appointing authority, or his or her delegate, may permit an employee to participate in a matter in which he or she has an otherwise disqualifying financial interest, if a waiver is issued based on a determination that the financial interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from the employee. As discussed below, I have decided to issue a conflict of interest waiver to permit you to participate in a certain particular matter.[1]

NATURE OF THE PARTICULAR MATTER

You, Walter Dunn, M.D., Ph.D., are a standing voting member of the Psychopharmacologic Drugs Advisory Committee (PDAC) and have been invited to serve at the joint meeting of the Drug Safety and Risk Management Advisory Committee (DSaRMAC) and the PDAC being held on November 19, 2024, to evaluate and discuss the reevaluation of the Clozapine Risk Evaluation and Mitigation Strategy (REMS) and possible changes to minimize burden on

[1] You are a federal government employee with the Department of Veteran Affairs. Therefore, waiver authority at 18 U.S.C. § 208(b)(3) related to the work of an SGE on a federal advisory committee does not apply to this waiver, which is being issued pursuant to 18 U.S.C. § 208(b)(l).

patients, pharmacies, and prescribers while maintaining safe use of clozapine. The topic of this advisory committee meeting is a particular matter involving specific parties.

EMPLOYEE'S POSITION, DUTIES AND ROLE

You are a federal government employee with the Department of Veteran Affairs. You serve as Director of the Mood Clinic and Interventional Psychiatry Service at the Greater Los Angeles Veterans Affairs (VA) Medical Center; Section Chief, Mood Disorders; and Staff Psychiatrist, Trauma Recovery Services at West Los Angeles VA Medical Center. You are also employed by the University of California, Los Angeles (UCLA) where you serve as an Assistant Clinical Professor at the Department of Psychiatry and as Faculty Director for the Psychiatry Residency Neuromodulation Concentration at the Semel Institute for Neuroscience and Human Behavior.

RELEVANT FACTORS CONSIDERED UNDER 18 U.S.C. § 208(b)(1)

In determining whether a waiver may be issued to allow your official participation in the particular matter described herein, I have considered each of the factors described in 5 C.F.R. § 2640.301(b), including the nature of the disqualifying financial interest as described above. I have also carefully considered the following additional factors:

1. *Value of the financial instrument or holding from which the disqualifying interest arises and relationship to your assets, and dollar value of the potential gain or loss due to resolution of the matter.*

You reported a financial interest in the ownership of publicly traded common stocks in (b) (6) has been identified as a party to the matter, due to their manufacture of clozapine Orally Disintegrating Tablets as well as (b) (6), which manufactures other clozapine tablets. The other six companies included in this waiver have been identified as firms having interests that may be affected by the particular matters at issue by the Center for Drug Evaluation and Research (CDER). At the writing of this waiver, the aggregate market value of your financial interests in the common stocks of all firms, (b) (6), is between $25,000 and $75,000. You own less than $15,000 worth of stock in (b) (6)

Under regulatory exemption 5 CFR § 2640.202(b) issued by the Office of Government Ethics, an employee may participate in any particular matter involving specific parties in which the disqualifying financial interest arises from the ownership by the employee, his spouse, or minor children, of securities issued by one or more entities that are competing/affected by the matter if the aggregate market value of the holdings of the employee, his spouse and minor children in the securities of all competing/affected entities does not exceed $25,000. Because your financial interests in the securities of all affected entities (whether or not a party to the matter) may exceed that amount, you have a disqualifying financial interest.

All of the companies listed above either have large, multi-billion-dollar market capitalizations or have several potential therapies in their pipeline for multiple different indications. There are a number of factors that mitigate the anticipated effect of this meeting on your financial interests. First, (b) (6) is one of 12 different clozapine manufacturers identified in FDA's "Orange Book" of approved drug products. Second, clozapine is one of over (b) (6) products that (b) (6) currently manufactures, reducing its overall impact on the firm. Third, it is a generic medication, which is typically associated with lower profit margins and thus lower overall impact on the firm's profitability. Fourth, clozapine's indicated use is for treatment-resistant (refractory) schizophrenia, which is a smaller patient population than that of schizophrenia patients overall. Finally, at this meeting, the PDAC and DSaRMAC are not reviewing clozapine's approval and thus feedback from this advisory committee meeting will not result in the submission or withdrawal of the drug from the market; rather, the topic of the meeting is the Clozapine REMS, which will affect only the logistical requirements to prescribe, dispense, and take the drug for prescribers, pharmacists, and patients, respectively.

Therefore, CDER does not anticipate that any action undertaken at this meeting will have any substantial effect on stock prices and does not anticipate their business interests will be significantly impacted by any competitive pressure arising from the meeting.

Finally, your overall financial holdings significantly outweigh any interests addressed by this waiver. The seven investments that are the subject of this waiver have a cumulative value well below 10% of your overall non-real estate investment interests.

2. *The Nature and Importance of Your Participation, and the Need for Your Services on the Matter.*

You have unique qualifications and specialized expertise needed for this particular matter. The upcoming PDAC meeting is focused on discussing the reevaluation of the Clozapine REMS and possible changes to minimize burden on patients, pharmacies, and prescribers while maintaining safe use of clozapine. Currently the Clozapine REMS involves regular blood testing for low white blood cell (neutrophils, specifically) counts, and concomitant registration and education efforts. The website explaining the REMS overall is available at newclozapinerems.com. This meeting will address potential changes and potential modifications to that REMS scheme to ensure that the costs of the REMS (including logistical frictions reducing access to the drug) are appropriately balanced against the risk of neutropenia among clozapine patients.

Clozapine is an atypical antipsychotic approved by the FDA for the treatment of individuals with treatment-resistant schizophrenia and for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder. It is the only FDA-approved medication for treatment-resistant schizophrenia.

A productive discussion of the issues regarding the reevaluation of the Clozapine REMS will depend upon having strong experts in the field of psychiatry, and the perspectives of multiple psychiatrists who have experience treating psychotic disorders such as schizophrenia will be critical for the thorough reevaluation of the Clozapine REMS program.

It is important to have multiple and potentially differing perspectives from psychiatrists, the medical specialists who are the primary prescribers of clozapine, on the benefits and challenges of the Clozapine REMS program. This will allow for a more robust and productive discussion of the issues.

Your professional background indicates that you have the relevant qualifications and specialized expertise needed for this particular matter. You are the Director of the Mood Clinic and Interventional Psychiatry Service at the Greater Los Angeles VA Medical Center, Section Chief, Mood Disorders, and Staff Psychiatrist, Trauma Recovery Services at West Los Angeles VA Medical Center. You are also an Assistant Clinical Professor at the UCLA Department of Psychiatry, Faculty Director for the UCLA Psychiatry Residency Neuromodulation Concentration at the Semel Institute for Neuroscience and Human Behavior at UCLA. Further, you are an attending physician in the UCLA Psychosis Clinic and Medical Co-Director psychiatrist for the UCLA Operation Mend Program.

Prior to your medical training, you completed a Doctor of Philosophy and post-doctoral work in molecular virology. You also served in the United States Marines. You completed your medical degree at UC Davis School of Medicine and completed your residency training at UCLA, Neuropsychiatric Institute. While in residency, you served as the Chief Resident of the residency research program and were the Chief Resident of the psychiatric intensive care unit at the Greater Los Angeles VA. During your residency, you trained at the UCLA Mood Disorders Clinic and UCLA Psychosis Clinic. You also trained in the Cognitive Behavioral Therapy (CBT) Clinic where you specialized in using CBT to treat anxiety disorders. You are board certified in Psychiatry and Neurology. Additionally, your research interests include developing novel neuromodulation treatments for psychiatric illnesses.

You provide a combination of expertise in neurobiology, clinical trial design and interpretation, and treatment of psychotic disorders. As a long-standing member of PDAC since 2017, you also have experience providing advice and recommendations on complex scientific issues that are pertinent to regulatory decision making. Accordingly, your professional experiences, combined with your previous experiences with advisory meetings as a standing member of the PDAC, will be invaluable to a robust and productive discussion on the issue coming before the committee.

3. *The Sensitivity of the Matter.*

This topic is considered to be sensitive, as the FDA Division with responsibility for the review of this product expects the matter coming before the committee to garner significant public interest, (non-trade) press interest, and significant congressional interest, and the matter is considered highly controversial.

4. *Your Expertise in this Particular Matter is Necessary in the Interest of Public Health.*

Schizophrenia is one of the top 15 leading causes of disability worldwide. In 2020, it was estimated that schizophrenia affects 1.1% of the population, or approximately 2.8 million adults in the United States (U.S.) aged 18 or older. Individuals with schizophrenia face an increased

risk of premature mortality, with the average potential life lost in the U.S. estimated at 28.5 years. Additionally, approximately 4.9% of people with schizophrenia die by suicide – a rate significantly higher than that of the general population, particularly during the early stages of the illness. Treatment-resistant schizophrenia, in which individuals do not respond to standard antipsychotic medications, occurs in approximately 30% of those diagnosed with schizophrenia.

Clozapine is recommended in the 2020 American Psychiatric Association treatment guidelines for individuals at a high risk of suicide, particularly when other treatments have not adequately reduced the risk of suicide attempts.

However, clozapine carries a risk of severe neutropenia, which can lead to life-threatening infections. As a result, FDA requires the implementation of the Clozapine REMS program to ensure patient safety. This monitoring is to mitigate the risk of life-threatening infections due to neutropenia.

In the interest of public health, it is important that the Agency has available the significant expertise that you will provide for the discussion of the particular matter before the committee.

DETERMINATION

Based on an evaluation of the factors in 5 C.F.R. § 2640.301(b), FDA has determined that your financial interests are not so substantial as to be deemed likely to affect the integrity of the services that the federal Government may expect from you. For the specific reasons detailed above, FDA grants you, Dr. Walter S. Dunn, a waiver under 18 U.S.C. § 208(b)(1) to permit you to participate in the advisory committee meeting described herein. This waiver is based on your full disclosure of your financial interests and consideration of the nature of the particular matter that you will be involved in as an FDA employee. This waiver only applies to the conflicts of interest described herein and for the joint meeting of the DSaRMAC and PDAC on November 19, 2024.

The Office of Government Ethics has been consulted concerning the issuance of this waiver, as specified in 5 C.F.R. § 2640.303, and the HHS Designated Agency Ethics Official has reviewed this document, as required by the Delegation of Authority by the Secretary to the Heads of Operating and Staff Divisions to Grant Conflict of Interest Waivers under 18 U.S.C. §§ 203(d), 205(e), and 208(b), dated January 16, 2009, and has concluded that this waiver adequately addresses the requirements for such waivers as set forth in OGE regulations at 5 C.F.R. § 2640.301.

Accordingly, I issue this waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a) based on the factors found at 5 C.F.R. § 2640.301(b).

CERTIFICATION

_____X___ The individual may participate, pursuant to 18 U.S.C. 208(b)(1) – The financial interest is not so substantial as to be deemed likely to affect the integrity of the services which the Government may expect from the employee.

Limitations on the Regular Government Employee's Ability to Act:

_____ Non-voting

_____ Other (specify):

_____

_____

_____ Denied – The individual may not participate.

_____ October 30, 2024
Robert M. Califf, M.D. Date
Commissioner of Food and Drugs

WALTER DUNN Digitally signed by WALTER DUNN
Date: 2024.10.30 06:17:58 -07'00'

_____ October 30, 2024
Walter Dunn, M.D., Ph.D. Date

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