U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM FOR WALTER DUNN, M.D., PH.D.

From: Robert M. Califf, M.D.
Commissioner
Food and Drug Administration (FDA)

Robert Califf -S
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Date: 2022.05.27 11:58 09 -04'00'

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

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 as described below.[1]

Nature of Disqualifying Financial Interest

The disqualifying financial interest at issue arises from your financial interests in the ownership of publicly traded common stocks in (b) (6) These companies have been identified as competing firms 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 $17,500 and $37,500.

Nature of the Particular Matter

You are a standing, voting member of the Psychopharmacologic Drugs Advisory Committee (PDAC). CDER would like to retain your services in participating in the PDAC meeting on June 17, 2022, to discuss supplemental new drug applications (sNDAs) 210793-s008 and

[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).

207318-s011, efficacy supplement resubmission for NUPLAZID (pimavanserin) tablets, submitted by Acadia Pharmaceuticals Inc., for the proposed treatment of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP). 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. The FDA has asked you to participate in the deliberations and voting at the advisory committee meeting described above.

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.

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.

The aggregate market value of your aggregate financial interests in the common stocks of (b) (6) is between $17,500 and $37,500. Under regulatory exemption(5 CFR § 2640.202(b)(2) 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 not parties to the matter but that are 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 affected entities does not exceed $25,000. Because your financial interests in stocks in these competing firms may exceed that amount, you have a disqualifying financial interest. Although the current value of your holdings may fall below the aggregate $25,000 de minimus value for non-party securities in 5 C.F.R. § 2640.202(b)(2), we are nonetheless issuing this waiver because, due to fluctuations in the stock market, the value of your holdings could rise above $25,000 at the time of the meeting.

With the exception of (b) (6), all of the companies listed above have large, multi-billion-dollar market capitalizations, and CDER does not anticipate that any action undertaken at this meeting will have any substantial effect on the stock price of (b) (6),

[redacted]. Similarly, CDER does not anticipate that [redacted] business interests will be significantly impaired by any competitive pressure arising from the meeting.

Regarding [redacted], while its market capitalization is respectively smaller than the other three interests, it represents a small, sub-$[redacted] portion of both the interests addressed by this waiver as well as your overall holdings. Additionally, [redacted] has a number of therapies it is developing, with its treatment for [redacted]. Any action undertaken at this meeting would not directly affect [redacted]; at most, it would expose [redacted] to increased competition.

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

The nature and importance of your participation, and the need for your services on the matter.

The advisory committee meeting that you will be participating in is focused on supplemental new drug applications (sNDAs) 210793-s008 and 207318-s011, efficacy supplement resubmission for NUPLAZID (pimavanserin) tablets, submitted by Acadia Pharmaceuticals Inc., for the proposed treatment of hallucinations and delusions associated with Alzheimer's disease psychosis (ADP).

Alzheimer's disease is the most common cause of dementia. The first symptoms of Alzheimer's disease are typically memory, language, and thinking problems. Alzheimer's disease is progressive and results in worsening cognitive function over time and reduced ability to carry out activities of daily living independently. According to the 2022 Alzheimer's Disease Facts and Figures (published by Alzheimer's Association), Alzheimer's disease remains the fifth leading cause of death among individuals aged 65 years and older. Alzheimer's disease is also a leading cause of disability and poor health in older adults. In 2021, family members and friends provided more than $271 billion in unpaid care to people living with Alzheimer's disease and other dementias.

According to the National Institute on Aging, experts suggest that more than 6 million Americans aged 65 years or older may have Alzheimer's disease and many more under age 65 years have the disease, although estimates vary. Although treatments are available to alleviate some of the illness's symptoms, there is no cure for the disease.

Neuropsychiatric symptoms are common in Alzheimer's disease. According to Meridien Research, psychosis affects between 40 and 50 percent of people with Alzheimer's disease at

some point over the course of the disease. About 36 percent of individuals with Alzheimer's disease report delusions and 18 percent experience hallucinations. Psychotic symptoms may speed up disease progression and increase the burden on caregivers. There are currently no FDA-approved medications for the treatment of Alzheimer's disease psychosis (ADP). Antipsychotic medications, more specifically atypical antipsychotics, are the most widely used off-label pharmacological treatment for ADP. Prescription drug labels for antipsychotic medications, including pimavanserin, contain a boxed warning to alert healthcare professionals about an increased risk of mortality associated with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. If approved for the indication under review, pimavanserin would be the only product approved to treat psychosis in Alzheimer's disease. 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 coming before the committee.

The advisory committee will discuss the adequacy of the submitted data to support the proposed indication for pimavanserin for the treatment of hallucinations and delusions associated with ADP. A productive discussion of the issues would depend upon having strong experts in the field of psychiatry, and the perspectives of multiple psychiatrists will be critical for the thorough evaluation of the efficacy data related to the use of pimavanserin in the ADP population. Psychiatrists on the advisory committee will be able to understand the condition of interest, ADP, the current treatment armamentarium, and how results of the clinical studies may translate to the clinical experience. Inclusion of more than one psychiatrist will increase the likelihood that these issues are fully explored during the discussion.

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 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 an Assistant Clinical Professor at University of California, Los Angeles (UCLA) Department of Psychiatry, Faculty Director for the UCLA Psychiatry Residency Neuromodulation Concentration and Associate Director, UCLA Psychiatry Continuing Medical Education (CME) Program at the Semel Institute for Neuroscience and Human Behavior at UCLA. 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 your 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.

Prescription drug labels for antipsychotic medications, including pimavanserin, contain a boxed warning to alert healthcare professionals about an increased risk of mortality associated with the use of atypical antipsychotics in elderly patients with dementia-related psychosis. If approved for the indication under review, pimavanserin would be the only product approved to treat psychosis in Alzheimer's disease, as no other approved drugs share the exact indication (treatment of ADP) under review. 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. 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 applications coming before the committee.

Sensitivity of the matter.

The FDA Division responsible for review of pimavanserin does expect the matter coming before the committee to garner public interest. It is considered a highly controversial issue with expected interest coming from non-trade press, congress, and the public. Alzheimer's disease is the most common form of dementia, affecting a significant number of Americans. There are currently no approved treatments for hallucinations and delusions associated with ADP, and antipsychotics are prescribed off-label in the community, which involve various risks including a boxed warning for an increased risk of death for elderly patients with dementia-related psychosis.

Determination

Based on my evaluation of the factors in 5 C.F.R. 2640.301(b), I have 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, I am granting you 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 your financial interests in [redacted] (b) (6) while serving on PDAC for the June 17 meeting.

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.

Please sign below indicating your agreement to the terms of this waiver and return the signed original to Russell Fortney, Director, Advisory Committee Oversight and Management, Office of the Chief Scientist, FDA, and retain a copy for your own records.

WALTER S. DUNN 715319

Digitally signed by WALTER S. DUNN 715319
Date: 2022 05.31 08 22:28 -07'00'

Walter Dunn, M.D., Ph.D.

5/31/22

Date

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