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

DATE: April 6, 2023

TO: Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

FROM: Byron Marshall
Director, Division of Advisory Committee and Consultant Management
Office of Executive Programs
Center for Drug Evaluation and Research

Name of Advisory Committee Meeting Temporary Voting Member: **Jacquelyn J. Maher, M.D.**

Committee: Gastrointestinal Drugs Advisory Committee

Meeting date: May 19, 2023

Description of the Particular Matter to Which the Waiver Applies:

Dr. Jacquelyn J. Maher is a temporary voting member of the Gastrointestinal Drugs Advisory Committee (GIDAC). The committee's function is to review and evaluate available data concerning the safety and effectiveness of marketed and investigational human drug products for use in the treatment of gastrointestinal diseases and make appropriate recommendations to the Commissioner of Food and Drugs.

On May 19, 2023, the committee will discuss new drug application (NDA) 212833, obeticholic acid 25 mg oral tablets, submitted by Intercept Pharmaceuticals, Inc., for the treatment of pre-cirrhotic liver fibrosis due to nonalcoholic steatohepatitis (NASH). The topic of this meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Maher reported a financial interest in [redacted] (b) (6), a healthcare sector mutual fund. The value of her holding in this fund is between $200,000 and $250,000. At the writing of this waiver, based on the most current publicly available information, this fund contains assets in competing firms: [redacted] (b) (6) representing generally less than 5.53% of the underlying holdings of the fund.

Under the regulatory exemption issued by the Office of Government Ethics (5 CFR § 2640.201(b)), an employee may participate in any particular matter affecting one or more holdings in a sector mutual fund where the disqualifying financial interest in the matter arises because of ownership of an interest in the fund and the aggregate market value of the interest in all funds in which there is a disqualifying financial interest, and which concentrates in the same sector, does not exceed $50,000. Because Dr. Maher's financial interest exceeds that amount, she has a disqualifying financial interest based on (b) (6) underlying investment holdings.

In addition, Dr. Maher's employing institution, Zuckerberg San Francisco General Hospital and Trauma Center, is participating in the pivotal study titled, *A Phase 3, Double-Blind, Randomized, Long-Term, Placebo-Controlled, Multicenter Study Evaluating the Safety and Efficacy of Obeticholic Acid in Subjects With Nonalcoholic Steatohepatitis (REGENERATE)*, NCT02548351, sponsored by Intercept Pharmaceuticals. The trial period is February 19, 2016, to (b) (4). While Dr. Maher is listed as a sub-investigator to ensure continuity of care in the event of a patient emergency with the site principal investigator unavailable, she has not been involved in the study and it is highly unlikely that she will be involved in the future.

Zuckerberg San Francisco General Hospital and Trauma Center has received in total between (b) (4). Dr. Maher does not receive salary support or personal remuneration from this funding.

Basis for Granting the Waiver:

Dr. Jacquelyn J. Maher has unique qualifications and specialized expertise needed for this particular matter.

Dr. Maher received her medical degree from Duke University School of Medicine followed by a residency in Internal Medicine, and Research Fellowship in Hematology. She is currently Chief of Gastroenterology at the University of California, San Francisco (UCSF), Zuckerberg San Francisco General Hospital; Professor and William and Mary Ann Rice Memorial Distinguished Professor at the School of Medicine at UCSF; and Director of the UCSF Liver Center.

Research in her laboratory focuses on the pathogenesis of nonalcoholic fatty liver disease (NAFLD). Her studies in mice have implicated dietary sugar as an important inducer of fatty liver disease, through conversion to toxic saturated fatty acids. Ongoing work in her group concentrates on the mechanism by which metabolic stresses kill liver cells. She is also using induced pluripotent stem cells (iPSCs) from patients with NAFLD to study the disorder directly in humans. Her research team has recently found that NAFLD iPSCs, when converted in the laboratory to hepatocytes (iPSC-Heps), display characteristics of NAFLD. The group is currently expanding their work with NAFLD iPSC-Heps to encompass larger populations from a variety of ethnic backgrounds. Given the safety concerns that have been identified in this application by the FDA Division with responsibility for review of this product, Dr. Maher will provide necessary expertise for this important discussion.

The particular matter is considered sensitive.

This topic is considered to be sensitive, as the FDA Division expects the meeting may receive significant public interest and non-trade press interest. Fatty liver disease has been more prominent in the press and obeticholic acid is the first drug seeking approval for this disease.

Dr. Maher's expertise in this particular matter is necessary in the interest of public health.

Nonalcoholic fatty liver disease (NAFLD), a condition in which excess fat is stored in the liver, is one of the most common causes of liver disease in the United States (U.S.). It's estimated that about 25% of adults in the U.S. have NAFLD and of those about 20% have NASH (5% of adults in the U.S.). The reason some people with NAFLD have simple fatty liver and others get NASH is not known, although research suggests that certain genes may play a role.

NASH is the more severe form of NAFLD in which an individual has inflammation of the liver and liver cell damage, in addition to fat in the liver. Inflammation and liver cell damage can also cause fibrosis which leads to permanent liver damage, cirrhosis, and its outcomes. The presence of metabolic syndrome (obesity, dyslipidemia, hypertension, and glucose intolerance) increases the likelihood that a patient has NASH rather than simple steatosis. The pathogenesis of NAFLD is poorly understood but seems to be linked to insulin resistance (e.g., as in obesity or metabolic syndrome). Obeticholic acid is the first drug seeking approval for NASH in the U.S.

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

Any potential for a conflict of interest is greatly outweighed by the strong need for Dr. Maher's expertise in this matter.

Dr. Maher is a hepatologist in practice for more than 20 years. She specializes in gastroenterology and internal medicine. Given her past and present professional and research experiences, Dr. Maher's participation in the committee's discussions will provide necessary expertise for this important discussion.

Accordingly, I recommend that you grant Dr. Jacquelyn J. Maher, a temporary voting member of the Gastrointestinal Drugs Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

✓ The individual may participate, pursuant to 18 U.S.C. 208(b)(3) – The need for the individual's services outweighs the potential for a conflict of interest created by the financial interest involved.

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.

Russell Fortney -S Digitally signed by Russell Fortney -S
Date: 2023.05.01 09:35:04 -04'00'

Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

May 1, 2023
Date