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

DATE: April 28, 2022

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 Temporary Voting Member: **Srinivasan Dasarathy, MD**

Committee: Pharmacy Compounding Advisory Committee

Meeting date: June 8, 2022

Description of the Particular Matter to Which the Waiver Applies:

Srinivasan Dasarathy, MD, is a temporary voting member of the Pharmacy Compounding Advisory Committee (PCAC). The committee's function is to provide advice on scientific, technical, and medical issues concerning drug compounding under sections 503A and 503B of the Federal Food, Drug, and Cosmetic Act, and, as required, any other product for which the Food and Drug Administration has regulatory responsibility and make appropriate recommendations to the Commissioner of Food and Drugs.

On June 8, 2022, the committee will discuss bulk drug substance, ammonium tetrathiomolybdate which is nominated for inclusion on the 503A Bulk List. The nominator of the substance or another interested party will be invited to make a short presentation supporting the nomination. Ammonium tetrathiomolybdate uses are evaluated for Wilson disease, use as copper (Cu) chelation therapy for the treatment of breast cancer, kidney cancer, prostate cancer, colorectal cancer, esophageal cancer, and malignant pleural mesothelioma.

The topic to be discussed during the meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Dasarathy reported that he and his spouse have financial interests in PPI healthcare sector mutual funds: [redacted] PPI

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[redacted] The aggregate market value of his and his spouse's holdings in these sector funds is between $100,000 to $150,000. At the writing of this waiver, based on publicly available fund information, no entity that is likely to be affected by the particular matter before the committee has been identified as a holding in these sector mutual funds. However, due to the changing nature of sector funds' holdings where underlying assets could include competing or affected entities, in the utmost of caution a waiver is sought for the funds [redacted] to ensure there is no recusal requirement on the day of the advisory committee meeting.

Under a regulatory exemption issued by the Office of Government Ethics at 5 C.F.R. § 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 interests 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. Dasarathy's financial interests in these healthcare sector mutual funds exceed that amount, he has a disqualifying financial interest.

Basis for Granting the Waiver:

Dr. Srinivasan Dasarathy has unique qualifications and specialized expertise needed for this particular matter.

Dr. Srinivasan Dasarathy is Professor of Medicine in the Cleveland Clinic Lerner College of Medicine, a Staff physician in the Departments of Gastroenterology and Hepatology, and a transplant hepatologist with a joint appointment with the Department of Inflammation and Immunity at the Cleveland Clinic Lerner Research Institute.

Dr. Dasarathy received his MB, BS in Medicine and M.D. from Jawaharlal Institute of Post Graduate Medical Education and Research and his D.M. from All India Institute of Medical Sciences. He is board certified in Internal Medicine and has practiced medicine for over 30 years.

Dr. Dasarathy is a highly regarded physician-scientist with invaluable expertise in the field of gastroenterology and hepatology. Dr. Dasarathy has written numerous peer reviewed publications on topics such as sarcopenia in liver disease, circulating biomarkers, microbiome, and outcomes in patients with liver disease, and liver cirrhosis. Additionally, Dr. Dasarathy is a reviewer for Hepatology, Journal of Hepatology, Liver Transplantation, American Journal of Gastroenterology, Journal of Clinical Gastroenterology, and the American Journal of Physiology. Dr. Dasarathy will bring to the meeting an expertise and a strong foundation in clinical research that are essential to the committee's discussion of ammonium tetrathiomolybdate.

The particular matter is sensitive.

This topic is considered to be sensitive as the FDA Division responsible for review of bulk drug substances does expect that the meeting is likely to receive significant public interest.

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

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State licensed pharmacy or a Federal facility, or a licensed physician, to be exempt from the following three sections of the FD&C Act: (1) Section 501(a)(2)(B) (21 U.S.C. 351(a)(2)(B)) (concerning current good manufacturing practice); (2) section 502(f)(1) (21 U.S.C. 352(f)(1)) (concerning the labeling of drugs with adequate directions for use); and (3) section 505 (21 U.S.C. 355) (concerning the approval of human drug products under new drug applications or abbreviated new drug applications).

One of the conditions that must be satisfied to qualify for the exemptions under section 503A of the FD&C Act is that a bulk drug substance (active pharmaceutical ingredient) used in a compounded drug product must meet one of the following criteria: (1) complies with the standards of an applicable United States Pharmacopoeia (USP) or National Formulary monograph, if a monograph exists, and the USP chapter on pharmacy compounding; (2) if an applicable monograph does not exist, is a component of a drug approved by the Secretary of Health and Human Services (the Secretary); or (3) if such a monograph does not exist and the drug substance is not a component of a drug approved by the Secretary, appears on a list developed by the Secretary through regulations issued by the Secretary (the ''503A Bulks List'') (see section 503A(b)(1)(A)(i) of the FD&C Act).

Copper is an essential microelement that plays an important role in biological processes. When it is imbalanced it can cause abnormalities. Copper is markedly elevated in Wilson disease and is believed to be elevated in cancer cells. Ammonium tetrathiomolybdate is an anticopper drug which acts as a copper chelator to interfere with intestinal uptake of copper when administered with meals and binds plasma copper when taken between meals. It is postulated that ammonium tetrathiomolybdate interferes with angiogenesis and reduces tumor growth. In the interest of public health, it is important that the Agency has available the significant expertise that Dr. Dasarathy 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. Srinivasan Dasarathy's expertise in this matter.

Dr. Dasarathy is the Principal Investigator (PI) and steering committee member in multiple NIH (National Institutes of Health) funded clinical research networks related to liver disease and function, including the NIAAA (National Institute on Alcohol Abuse and Alcoholism) funded DASH (Defeat Alcoholic Steatohepatitis) consortium that transitioned to the Alcoholic Hepatitis network (AlcHep Network), NIDDK (National Institute of Diabetes and Digestive and Kidney Diseases) funded non-alcoholic steatohepatitis clinical research network (NASH CRN), the Liver Cirrhosis Network (LCN), and PI of a research component of the NIAAA P50 Northern Ohio Alcohol Center. He has developed and completed human studies in patients with various liver diseases including those with cirrhosis. Dr. Dasarathy also leads the liver transplant nutrition clinic at the Cleveland Clinic and has established an inpatient nutrition program for the management of hospitalized cirrhotic patients. He also coauthored recent EASL (European

Association for the Study of the Liver) and ESPEN (European Society for Parenteral and Enteral Nutrition) guidelines on Nutrition and Liver Diseases and the AASLD (American Association for the Study of Liver Diseases) guidance on malnutrition, frailty, and sarcopenia in liver disease. He is also a member of the American College of Gastroenterology guidelines committee on Nutrition in Liver Disease.

As a practicing hepatologist caring for patients with end stage liver disease, Dr. Dasarathy brings a wealth of knowledge and hands-on experience that will be invaluable to the committee. Given that this is a very focused issue, Dr. Dasarathy is highly qualified to provide insight and feedback on the use of ammonium tetrathiomolybdate for Wilson Disease and whether the Agency should permit its use in compounding by adding it to the 503A Bulks List.

Accordingly, I recommend that you grant Dr. Srinivasan Dasarathy, a temporary voting member of the Pharmacy Compounding 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: 2022.05.18 07:33:42 -04'00'

May 18, 2022

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

Date