



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

DATE: May 12, 2021

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: **Suthat Liangpunsakul, MD, MPH**

Committee: Pharmacy Compounding Advisory Committee (PCAC)

Meeting date: June 9, 2021

Description of the Particular Matter to Which the Waiver Applies:

Suthat Liangpunsakul, MD, MPH, 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 9th, the committee will discuss bulk drug substances nominated for inclusion on the 503A Bulks List. The nominators of these substances or another interested party will be invited to make a short presentation supporting the nomination. One of the bulk substances to be discussed is choline chloride (uses are for liver diseases (including non-alcoholic fatty liver disease), hepatic steatosis, atherosclerosis, fetal alcohol spectrum disorder, and supplementation in long term total parenteral nutrition). The topic to be discussed during the meeting is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Liangpunsakul reported that he and his spouse have a financial interest in [REDACTED] (b) (6), a medical technology and device sector mutual fund. The value of the holdings in this fund is between \$250,000 and \$350,000. At the

writing of this waiver, based on publicly available fund information, the sector fund contains assets in (b) (6), representing (b) (6) % and (b) (6) % respectively of the underlying value of the fund.

Under a regulatory exemption (5 CFR § 2640.201(b)) issued by the Office of Government Ethics, 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 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. Liangpunsakul's financial interest in the (b) (6) exceeds that amount, he has a disqualifying financial interest based on the fund's holdings of (b) (6).

Basis for Granting the Waiver:

Dr. Suthat Liangpunsakul has unique qualifications and specialized expertise needed for this particular matter.

Dr. Suthat Liangpunsakul received his medical degree from Prince of Songkhla University, Songkhla, Thailand, and his Fellowship in gastroenterology and hepatology from Indiana University School of Medicine, Indianapolis, Indiana. He received his Master of Public Health degree from Indiana University Purdue University Indianapolis (IUPUI). He is board certified in gastroenterology and transplant hepatology. Dr. Liangpunsakul is an Academic Co-Director in the Division of Gastroenterology and Hepatology, Department of Medicine at Indiana University School of Medicine. He is a Professor of Medicine, Biochemistry and Molecular Biology and Dean's Scholar at Indiana University School of Medicine. He is Associate Chief of Staff for Research and Staff Physician, Roudebush Veterans Administrator Hospital and Staff Physician at Indiana University Health, IU Hospital Center and Eskenazi Hospital. His research focuses on the identification of non-invasive biomarkers to screen for excessive alcohol use and the molecular mechanism, risk factors, and treatment for alcohol-induced liver injury.

Dr. Liangpunsakul is a senior tenured professor who is a highly regarded physician-scientist and a thought leader in the field. He has written/co-authored more than 150 peer-reviewed articles and six book chapters. He is also the standing member of the National Institutes of Health/Hepatobiliary Pathophysiology (NIH/HBPP) study section. In addition, he is an editorial board member of Hepatology, Hepatology Communications, and Alcoholism: Clinical and Experimental Research. Dr. Liangpunsakul is a fellow of the American Gastroenterological Association (AGA) and the American College of Gastroenterology (ACG). He is also a Fellow of the American Association for the Study of Liver Diseases (AASLD) and currently serves as a member on AASLD Research Awards Committee. During his tenure at Indiana University, he was awarded the prestigious Indiana University Trustee Teaching Award in 2011 and Showalter Scholar in 2017. He was the past President of the American Federation for Medical Research (AFMR). In May 2019, he was appointed as the Associate Chief of Staff for Research at the Roudebush Veterans Administration Medical Center.

The particular matter is sensitive.

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

Dr. Suthat Liangpunsakul'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).

The Agency is evaluating choline chloride (Choline) to determine whether or not to include this substance on the 503A Bulks List. Choline is an essential nutrient that supports vital bodily functions. It was recognized as a required nutrient by the United States Institute of Medicine in 1998, and guidelines regarding the daily adequate intake for various age-groups and a tolerable upper intake limit were established. The liver is an important organ for metabolism and storage of Choline, and liver is dependent on a source of Choline. Choline can be obtained from foods in the diet and dietary intake of Choline needs varies among individuals. Men and postmenopausal women experience signs of organ dysfunction with insufficient dietary Choline.

Choline also supports numerous vital bodily functions including cellular maintenance, deoxyribonucleic acid (DNA) synthesis, metabolism, and nervous system functioning. Choline is necessary to produce fats that make up cellular membranes and it also helps metabolize fat. Choline along with other nutrients affect gene expression. The body converts Choline into a neurotransmitter that affects the nerves and plays a role in regulating automatic bodily functions, such as breathing and heart rate. Choline has been suggested to both protect and increase the risk of cardiovascular disease (CVD) and may also help to reduce blood pressure and stroke.

There is a link between Choline deficiency and liver disease. Liver diseases can lead to liver

cancer or liver failure. Excess fat stored in the liver can lead to nonalcoholic fatty liver disease (NAFLD), a common chronic liver disease that is characterized by simple steatosis (fat accumulation in the liver), steatohepatitis (liver inflammation and damage caused by a buildup of fat in the liver), hepatic fibrosis (healthy tissue of the liver becomes scarred), and cirrhosis (severe scarring of the liver with permanent damage). NAFLD is associated with systemic metabolic disorders, including obesity, type II diabetes mellitus, atherosclerosis, and dyslipidemia, and is considered to be the hepatic component of metabolic syndrome. NAFLD is the most common liver condition worldwide, affecting up to 30% of Western populations. The disease is influenced by nutrition and genetics; current treatment is based on reducing body fat through caloric restriction and physical activity. Supplemental choline has been found to prevent NAFLD and maintaining adequate dietary Choline intake helps prevent fatty liver disease. Further, patients who receive total parenteral nutrition (nutrition through the vein), can develop Choline deficiency, which can lead to hepatic steatosis. Intravenous Choline has been used to treat and prevent hepatic steatosis in patients that receive total parenteral nutrition.

During fetal development, Choline influences stem cell proliferation and apoptosis, also known as programmed cell death, which is essential for brain and spinal cord structure and function, decreasing neural tube defects and increasing memory function. Maternal nutrition can often be compromised when alcohol is consumed, especially in situations of chronic alcoholism. Poor overall nutrition may contribute to and/or compound the effects of prenatal alcohol exposure. Fetal alcohol spectrum disorders (FASDs) represent a profound public health crisis with prevalence estimates as high as 2–5% in the United States and Western Europe. Individuals with fetal alcohol syndrome (FAS), which is the most severe form of FASD, have high rates of intellectual impairment. Individuals with other FASDs, including partial fetal alcohol syndrome (pFAS) and alcohol-related neurodevelopmental disorder, are seriously affected by deficits in attention, executive functioning, and memory among other skills. There are few cognitive and behavioral interventions for FASDs, and there are no biological treatments. In the interest of public health, it is important that the Agency has available the unique expertise in gastroenterology and hepatology that Dr. Liangpunsakul 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. Suthat Liangpunsakul's expertise in this matter.

Dr. Liangpunsakul is a senior tenured professor, highly regarded physician-scientist, and a highly productive and innovative thought leader in the fields of gastroenterology and hepatology. With a strong foundation as a researcher and clinician in gastroenterology and hepatology, Dr. Liangpunsakul is uniquely qualified to provide insight and feedback on the uses of choline chloride for liver diseases (including non-alcoholic fatty liver disease) and hepatic steatosis and whether the Agency should permit its use in compounding by adding it to the 503A Bulks List. Dr. Liangpunsakul's expertise in gastroenterology and hepatology are essential to the committee's discussion.

Accordingly, I recommend that you grant Dr. Suthat Liangpunsakul, 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
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Russell Fortney
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

May 19, 2021
Date