



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

DATE: May 25, 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 Standing Voting Member: **Kathleen Gura, PharmD, BCNSP**

Committee: Pharmacy Compounding Advisory Committee

Meeting date: June 9, 2021

Description of the Particular Matter to Which the Waiver Applies:

Kathleen Gura, PharmD, BCNSP, is a standing 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 9, 2021, the committee will discuss bulk drug substances nominated for inclusion on the 503A Bulk List. The nominators of these substances or another interested party will be invited to make a short presentation supporting the nomination. The four bulk drug substances to be discussed are choline chloride (uses are for the treatment of liver diseases (including non-alcoholic fatty liver disease), hepatic steatosis, atherosclerosis, fetal alcohol spectrum disorder, and supplementation in long term total parenteral nutrition); melatonin for the treatment of sleep disorders in patients with autism spectrum disorder (specifically children and adolescents); methylcobalamin uses are evaluated for amyotrophic lateral sclerosis (also known as ALS), pain management, peripheral neuropathy (including diabetic neuropathy), inborn errors of metabolism (also known as genetic metabolic disorders) (including methylenetetrahydrofolate reductase deficiency (also known as MTHFR)), hyperhomocysteinemia (including conjunctive therapy in

hemodialysis patients), vitamin B12 deficiency, and autism spectrum disorder; and oxitriptan (5-HTP) for the treatment for patients with tetrahydrobiopterin (BH4) deficiency.

The committee will also discuss revisions FDA is considering to the Withdrawn or Removed List. FDA now is considering whether to amend the rule to add one more entry to the list: Neomycin Sulfate: All parenteral drug products containing neomycin sulfate (except for ophthalmic or otic use, or when combined with polymyxin B sulfate for irrigation of the intact bladder). As previously explained in the Federal Register of July 2, 2014 (79 FR 37687 at 37689 through 37690), the list may specify that a drug may not be compounded in any form, or, alternatively, may expressly exclude a particular formulation, indication, dosage form, or route of administration from an entry on the list. Moreover, a drug may be listed only with regard to certain formulations, indications, routes of administration, or dosage forms because it has been found to be unsafe or not effective in those particular formulations, indications, routes of administration, or dosage forms. FDA plans to seek the committee's advice concerning the inclusion of this drug product on the list.

The topics to be discussed during the meeting are particular matters involving specific parties.

Type, Nature, and Magnitude of the Financial Interest:

Dr. Gura reported that her spouse holds stock in (b) (6) that provides compounding services for drug products and could be financially affected by the discussions of the Bulk Drug Substances at issue. The value of the holdings in this security is between \$50,000 to \$100,000. Under a regulatory exemption issued by the Office of Government Ethics at 5 C.F.R. § 2640.202(b), an employee may participate in any particular matter involving specific parties in which the disqualifying financial interest arises from the ownership 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 in the securities of all affected entities does not exceed \$25,000. Because Dr. Gura's financial interest in (b) (6) exceeds that amount, she has a disqualifying financial interest.

Basis for Granting the Waiver:

Dr. Kathleen Gura has unique qualifications and specialized expertise needed for this particular matter.

Dr. Kathleen Gura is the Pharmacy Clinical Research Program Manager and a clinical pharmacist with the Clinical Nutrition Service at Boston Children's Hospital. She is also an Assistant Professor of Pediatrics at Harvard Medical School, Associate Professor at Massachusetts College of Pharmacy and Health Sciences (MCPHS), and an adjunct member of the faculty at Northeastern University, University of North Carolina at Chapel Hill, and University of Connecticut.

Dr. Gura received her Bachelor of Science in Pharmacy and Doctor of Pharmacy from the Massachusetts College of Pharmacy and Health Sciences in Boston, with high honors. Board certified as a Nutritional Support Pharmacist, Dr. Gura is a Fellow of the American Society for

Health System Pharmacists (ASHP), American Society for Parenteral and Enteral Nutrition (ASPEN), Pediatric Pharmacy Association (PPA) and Massachusetts Society of Health System Pharmacists (MSHP). She served as president of the Massachusetts Society of Health System Pharmacists and is currently serving on the Board of Directors for ASPEN.

Her professional focus is on academic clinical pharmacy and research, and her topics of expertise include nutritional support for the critically ill pediatric patient, nutritional support in intestinal failure, intravenous lipid emulsions and sterile products preparation. Dr. Gura is the author of numerous book chapters on pediatric nutrition and has written more than 130 peer-reviewed articles on topics such as the parenteral nutrition (PN) associated cholestasis, clinical practice guidelines for parenteral nutrition, and the use of parenteral nutrition in the neonate. She currently serves as a consultant/subject matter expert for (b) (4)

Dr. Gura was awarded the American Society for Health System Pharmacists (ASHP) Drug Therapy Research Award as well as the Outstanding Pharmacist and Serlick Award for Safe Practices and was recently named the 2020 Nutrition Champion by ASPEN. Her research focuses on parenteral nutrition associated liver disease, intestinal failure, and lipid emulsions. Her work has been funded by the March of Dimes and the FDA's Orphan Drug Development Program. Dr. Gura's broad knowledge and experiences, from nutritional support for the critically ill pediatric patient, nutritional support in intestinal failure, intravenous lipid emulsions, and preparation of sterile products are crucial for the topics that will be discussed at the meeting. Her input will be invaluable and result in an enhanced, in-depth dialog.

The particular matter is sensitive.

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

Dr. Kathleen Gura'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 bulk drug 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. Gura will provide for the discussion of the particular matter before the committee.

The Agency is evaluating melatonin to determine whether or not to include this bulk drug substance on the 503A Bulks List. Melatonin is a natural hormone that is produced by the pineal gland in the brain and then released into the bloodstream. Melatonin made by the body is known as endogenous melatonin and it facilitates a transition to sleep. Melatonin helps regulate circadian rhythm and synchronize the sleep-wake cycle with night and day. The hormone can also be made synthetically, known as exogenous melatonin, as a dietary supplement. Melatonin supplement is used for sleep disorders such as insomnia and jet lag. It is also used as a sleep aid for children with autism spectrum disorder (ASD).

The Centers for Disease Control and Prevention (CDC) reported that approximately 1 in 54 children in the United States is diagnosed with ASD. Sleep disturbances are endemic among children with ASD. Studies have estimated the prevalence of sleep disturbance as 40% to 80% in children with ASD, compared to 20% to 40% in typically developing children. Children with sleep problems and insufficient sleep can result in daytime sleepiness, learning problems and behavioral issues such as hyperactivity, inattentiveness and aggression. Children with ASD who are poor sleepers exhibit more problematic behavior than good sleepers.

The Agency is evaluating methylcobalamin to determine whether or not to include this bulk drug substance on the 503A Bulks List. Vitamin B12 is a nutrient that helps keep the body's nerve and blood cells healthy and helps make deoxyribonucleic acid (DNA), the genetic material in all cells. Vitamin B12 also helps prevent a type of anemia called pernicious anemia, a type of megaloblastic anemia that makes people tired and weak. A deficiency in this vitamin can cause serious symptoms, including fatigue, nerve damage, digestive issues, and neurological problems like depression and memory loss. Vitamin B12 deficiency is seen most commonly in elderly patients with age-related changes in vitamin absorption, and in people whose diets do not include animal products. Vitamin B12 dietary supplements are typically derived from two sources: cyanocobalamin or methylcobalamin.

Cyanocobalamin is a synthetic form of vitamin B12 only found in dietary supplements while methylcobalamin is a naturally occurring form of vitamin B12 that can be obtained through either food sources or supplements. FDA approved prescription drug products contain cyanocobalamin or hydroxocobalamin. Both are approved for treatment of vitamin B12 deficiency.

Amyotrophic lateral sclerosis (ALS) is a group of rare neurological diseases that mainly involve the nerve cells (neurons) responsible for controlling voluntary muscle movement. Voluntary muscles produce movements like chewing, walking, and talking. The disease is progressive, and the cause of ALS is not known; there is no cure for or effective treatment to halt or reverse the

progression of the disease. In 2016 the CDC estimated that between 14,000 to 15,000 Americans have ALS and it affects people of all races and ethnic backgrounds. Currently there are only two FDA approved drugs to treat some symptoms of ALS, riluzole (Rilutek) and edaravone (Radicava). In mice, ultra-high doses of methylcobalamin was shown to attenuate motor symptoms, inhibit denervation muscle atrophy and motor axonal loss, and elevate vitamin B12 levels in sera, muscles, and spinal cord. Methylcobalamin has been used as a parenteral supplement for patients with ALS although its role in ALS treatment remains under investigation.

Neuropathic pain describes a range of unpleasant sensations caused by neuropathy, a lesion or disease of the somatosensory nervous system. The sensations caused by neuropathic pain are debilitating and improved treatment regimens are sought in order to improve the quality of life of patients with diabetic neuropathic pain, subacute herpetic neuralgia, glossopharyngeal neuralgia, and trigeminal neuralgia. Vitamin B12 is thought to alleviate pain in neuropathy conditions by a number of mechanisms including promoting myelination, increasing nerve regeneration and decreasing ectopic nerve firing. Methylcobalamin has been used as an analgesic drug in nonspecific low back pain and neck pain. The effectiveness of methylcobalamin in these conditions remains under investigation.

Inborn errors of metabolism are rare genetic disorders in which the body cannot properly turn food into energy. The disorders are usually caused by defects in specific proteins that help break down parts of food. Several inborn errors of metabolism cause developmental delays or other medical problems if they are not controlled. Homocystinuria, methylmalonic aciduria, and a condition in which both enzyme deficiencies exist are examples of inborn errors of metabolism that can be responsive to treatment with vitamin B12. Hyperhomocysteinemia, which is not an inborn error of metabolism, can result from folic acid deficiency. Hyperhomocysteinemia affects about 5% of the general population. Elevated homocysteine levels are associated with increased risk cardiovascular issues such as stroke, heart attack, peripheral arterial disease, and narrowing of the extracranial carotid artery. Hyperhomocysteinemia occurs in about 85% of chronic kidney patients because of impaired renal metabolism and reduced renal excretion. Reduced kidney function is associated with an increased risk for cardiovascular events and mortality. Elevated homocysteine levels can be treated by folate supplementation, sometimes given with vitamin B12 if a dietary deficiency exists.

Autism spectrum disorder (ASD) is a behaviorally defined disorder that is estimated to affect up to 1 in 45 individuals in the United States. ASD encompasses the wide range of clinical symptoms seen in those individuals whom have been diagnosed with some form of autism. Behavioral assessments often note inattention, aggression, impulsivity, hyperactivity, excessive compulsions, affective instability, and occasional psychosis in autistic children. This disorder is difficult to diagnose and treat using pharmacological therapy. Atypical antipsychotics, selective serotonin reuptake inhibitors and psychostimulants have all shown some clinical benefits in this disorder, but they are often associated with significant side effects. Alternative pharmacological therapies, like nutritional interventions and vitamin/mineral supplements, can correct abnormal transmethylation and transsulfuration pathways, increase anti-oxidant capacity and possibly improve autistic behavior in a safer way with less side effects and better tolerability. There is growing evidence that ASD is associated with abnormalities in several metabolic pathways,

including the inter-connected folate, methylation and glutathione pathways. ASD has been linked to increased levels of oxidative stress and lower anti-oxidant capacity. Methylcobalamin has the unique ability to directly activate the transmethylation and transsulfuration pathways. As the theoretical basis for use of methylcobalamin, it is posited that some children with autism may have lower levels of methyltransferase enzyme, and therefore do not create enough methylcobalamin. Treatment with supplemental methylcobalamin, folic acid, and/or sapropterin, a synthetic form of tetrahydrobiopterin (BH4), have the potential to positively affect folate, methylation and glutathione pathways.

The Agency is evaluating oxitriptan to determine whether or not to include this bulk drug substance on the 503A Bulks List. Tetrahydrobiopterin (BH4) deficiency is a rare disorder that causes the body to build up an abnormally high amount of the amino acid phenylalanine, one of the building blocks of protein. The BH4 deficiency also leads to low levels of certain neurotransmitters, chemical messengers that control many body functions. Babies with BH4 deficiency appear normal at birth but may develop neurological symptoms such as abnormal muscle tone, poor head control, seizures, and delayed motor development. Without treatment, the condition can cause permanent intellectual disability. The BH4 deficiency affects males and females in equal numbers and has been diagnosed in a diversity of ethnic groups worldwide. In the United States, the disorder is estimated to affect 1% to 3% of infants diagnosed with high levels of phenylalanine by newborn screening. The BH4 deficiency is estimated to affect approximately 1 in 1,000,000 individuals in the general population.

The BH4 deficiency is caused by a mutation in specific genes. The four main forms of BH4 deficiency are: guanosine triphosphate cyclohydrolase I (GTPCH) deficiency; 6-pyruvoyl tetrahydropterin synthase (PTPS) deficiency; pterin-4- α -carbinolamine dehydratase (PCD) deficiency; and dihydropteridine reductase (DHPR) deficiency. The first two disorders are defects in tetrahydrobiopterin creation and the latter two are defects in tetrahydrobiopterin regeneration. Depending on the form of BH4 deficiency, treatment may consist of tetrahydrobiopterin supplementation and diet to control phenylalanine intake. Treatment may also require restoring neurotransmitter balance with a regimen of amine neurotransmitter precursors, which are substances that are converted into specific neurotransmitters by enzymes in the blood and brain. Specific precursors used to treat BH4 deficiency are oxitriptan (5-HTP) and levodopa (L-dopa) along with carbidopa. In most cases, supplemental therapy with neurotransmitter precursors is required for life.

In addition, one of the conditions that must be satisfied to qualify for the exemptions under section 503A or section 503B of the FD&C Act is that the drug that is compounded does not appear on a list published by the Secretary of drugs that have been withdrawn or removed from the market because such drug products or components of such drug products have been found to be unsafe or not effective (“Withdrawn or Removed List”) (see sections 503A(b)(1)(C) and 503B(a)(4) of the FD&C Act). The Withdrawn or Removed List is codified at 21 CFR 216.24.

Neomycin sulfate is a broad-spectrum aminoglycoside antibacterial drug that acts through inhibition of bacterial synthesis. Neomycin sulfate is poorly absorbed from the normal gastrointestinal tract. The small absorbed fraction is rapidly distributed in the body tissues and is excreted by the kidney. The unabsorbed portion of the drug (approximately 97%) is eliminated

unchanged in the feces. As with other aminoglycosides, the amount of systemically absorbed neomycin sulfate transferred to the tissues increases cumulatively with each repeated dose administered until a steady state is achieved. The kidney is the primary excretory path as well as a site of tissue binding, with the highest concentration found in the renal cortex. Progressive accumulation also occurs in the inner ear. Systemic exposure to neomycin sulfate can induce significant toxicity in the kidneys, toxicity in the inner ear that can manifest as hearing loss, and neuromuscular blockade.

In the interest of public health, it is important that the Agency has available the unique expertise in parenteral nutrition, pediatrics, and sterile compounding that Dr. Gura will provide for the discussions of the particular matter before the committee.

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

Dr. Gura's expertise in pediatrics will be invaluable to the discussions on choline chloride, melatonin, methylcobalamin, and oxitriptan. Her research focus on parenteral nutrition associated liver disease will be directly applicable when choline chloride is discussed. Her professional focus and expertise in nutritional support for the critically ill pediatric patients means she will be able to handle the questions and provide advice the Agency seeks during the upcoming meeting. Through her roles as a Pharmacy Clinical Research Program Manager, a clinical pharmacist with the Clinical Nutrition Service at Boston Children's Hospital, Assistant Professor of Pediatrics at Harvard Medical School and a Fellow of the Pediatric Pharmacy Association (PPA), Dr. Gura is in a unique position to provide insights into the treatment of children and adolescents.

Dr. Gura's experience in sterile compounding will be invaluable during the AC's consideration of neomycin sulfate. Dr. Gura has worked as a Sterile Products Manager for the Boston Children's Hospital, Department of Pharmacy, and has taught on sterile-products pharmacy practice. In 2014 and 2017, Dr. Gura authored peer-reviewed articles on sterile-product compounding. In addition, her focus on toxicity associated with parenteral administration of nutrition may provide valuable insight on the toxicities associated with the parenteral administration of neomycin sulfate. Other members of the PCAC do not have Dr. Gura's professional focus regarding toxicity associated with parenteral administration. Dr. Gura is able to provide the committee with necessary expertise regarding toxicity concerns associated with parenteral administration of neomycin sulfate and whether FDA should prevent its use in compounding by adding it to the Withdrawn or Removed List.

Dr. Gura's demonstrated experiences will provide significant value in the committee's consideration of these topics. Dr. Gura has specialized expertise in pediatric patient populations that other members of the committee do not possess. Although there are other pharmacists who are members of this committee, having multiple committee members who are pharmacists with experience in human drug compounding ensures that the committee will be able to provide relevant and meaningful advice on human drug compounding for the FDA to use in its pursuit of protecting the public health. Dr. Gura's expertise in pediatrics, gastrointestinal medicine, sterile

compounding, hepatology, and parenteral nutrition are unique and highly relevant to the topics that will be discussed at the advisory committee meeting on June 9, 2021.

Accordingly, I recommend that you grant Dr. Kathleen Gura, a 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: 2021.05.25 17:37:25 -04'00'

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

May 25, 2021
Date