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

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

Committee: Pharmacy Compounding Advisory Committee

Meeting date: June 8, 2022

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 8, 2022, 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 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); enclomiphene citrate (to increase serum testosterone, luteinizing hormone (LH), and follicle-stimulating hormone (FSH) to normal levels in the treatment of secondary hypogonadism); ferric subsulfate (for use as an astringent and hemostatic agent during minor surgical procedures); and glutathione (uses are evaluated for skin lightening, cystic fibrosis, asthma, chronic obstructive pulmonary disease, chronic lung disease, oxidative stress, reduction of the side effects of chemotherapy, inhibition of chemical induced carcinogenesis, prevention of radiation injury, treatment of heavy metal poisoning (cadmium and mercury), acetaminophen toxicity, autism spectrum disorder,

Alzheimer's disease, Parkinson's disease, major depressive disorder, schizophrenia, helicobacter pylori infection, human immunodeficiency virus infection, tuberculosis, otitis media, peripheral obstructive arterial disease, anemia, diabetes, and septic shock).

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 the following entry to the list: lorcaserin hydrochloride. 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 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 [redacted]PPI operates [redacted]PPI 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 [redacted]PPI 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 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 150 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 Wolters Kluwer-Kelly (Lexicomp).

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 expertise in pediatrics, gastrointestinal medicine, sterile compounding, hepatology, and parenteral nutrition are highly relevant to 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 FDA 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).

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.

Enclomiphene citrate is a selective estrogen receptor modulator (SERM) that is thought to compete with estrogen for estrogen receptor binding sites, limiting suppression of release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the pituitary and increasing testosterone levels. Secondary hypogonadism stems from a disruption of the hypothalamic-pituitary-gonadal (HPG) axis.

Ferric subsulfate is a hemostatic agent that causes agglutination of surface proteins resulting in local hemostasis. Local hemostasis induces wound healing targeted to the site of injured vessels and innate wound response following bleeding (blood loss, hemorrhage). Topical hemostatic agents most commonly are used in situations where the use of electrocautery or sutures for hemostatic control of surgical bleeding is not ideal or safe. Different sources define ferric subsulfate as an astringent, hemostatic, or styptic agent.

Glutathione is a tripeptide (γ-L-Glutamyl-L-cysteinyl-glycine) that is endogenously synthesized in the human body. The compound can also be synthesized exogenously. Although glutathione is synthesized from precursor amino acids in virtually all cells, the liver is the main source of plasma glutathione. The main function of glutathione is as an antioxidant. Glutathione is an essential cofactor for numerous enzymes including the glutathione peroxidases and glutathione S-transferases in reactions that occur to inactivate various exogenous toxins (e.g., xenobiotics, environmental toxins, pharmaceuticals).

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.

Lorcaserin is a 5-hydroxytryptamine (5-HT2C) agonist which is a type of serotonin receptor agonist. It was approved by the FDA in 2012 and was indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in obese adults or overweight patients with at least one weight-related comorbid condition. Lorcaserin works by increasing feelings of fullness so that less food is eaten. In February 2020 FDA requested that lorcaserin be withdrawn because a safety clinical trial shows an increased occurrence of cancer.

In the interest of public health, it is important that the Agency has available the combined 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 experience in hepatology and pediatrics will be invaluable during the advisory committee's discussion of ammonium tetrathiomolybdate, enclomiphene citrate, glutathione, and ferric subsulfate. Her research focusses on liver disease and will be directly applicable during discussions on hepatic impairment and enclomiphene citrate at the upcoming meeting. As a Pharmacy Clinical Research Program Manager and a clinical pharmacist with the Clinical Nutrition Service at Boston Children's Hospital, Dr. Gura is in a position to provide necessary insight into the treatment of children and adolescents with conditions listed previously.

Dr. Gura's clinical research experience in sterile drug compounding will be invaluable during the advisory committee's consideration of lorcaserin hydrochloride. 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 2021, Dr. Gura was a panel member at the Institute for Safe Medication Practice (ISMP) Sterile Compounding Technology Safety Summit. She earned a certificate in medical writing from the University of Connecticut and is currently the Pharmacy Clinical Research Manager at Boston Children's Hospital. Her significant experience highlights her strong ability to interpret medical literature and research. This is a skill that will enable her to provide perspective on the lorcaserin hydrochloride topic at the advisory committee meeting. Dr. Gura is likely to grasp the safety information and available data related to the withdrawal of lorcaserin hydrochloride. Dr. Gura's broad range of relevant experience enables her to add a valuable perspective on whether FDA should prevent its use in compounding by adding it to the Withdrawn or Remove 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 strong foundation in gastrointestinal medicine and sterile products compounding, clinical trials, and her vast experiences as a clinical pharmacist, educator, and clinical researcher are essential to the advisory committee's enhanced and in-depth discussion at the advisory committee meeting on June 8, 2022.

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):

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_____ Denied – The individual may not participate.

Russell Fortney -S Digitally signed by Russell Fortney -S Date: 2022.05.18 07:29:36 -04'00'

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

May 18, 2022
Date