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

DATE: September 23, 2024

TO: Emily Helms Williams
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 Standing Member: **Padma Gulur, MD**

Committee: Pharmacy Compounding Advisory Committee

Meeting Date: October 29, 2024

Description of the Particular Matter to Which the Waiver Applies:

Padma Gulur, MD, has been invited to serve as a standing voting member and Chairperson of the Pharmacy Compounding Advisory Committee (PCAC). Dr. Gulur is a special Government employee serving on an advisory committee under the Federal Advisory Committee Act (5 U.S.C. 1001 *et seq.*). 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 October 29, 2024, the Committee will discuss bulk drug substances being considered for inclusion on the 503A Bulks List. The nominators of these substances will be invited to make a short presentation supporting the nomination. The four bulk drug substances to be discussed are ibutamoren mesylate (uses are for the treatment of growth hormone deficiency (GHD), osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease (AD); L-theanine (for the treatment of sleep disorders and anxiety disorders); ipamorelin-related bulk drug substances, ipamorelin acetate and ipamorelin (free base) (for the treatment of GHD and postoperative ileus); and kisspeptin-10 (for the treatment of secondary hypogonadism in men).

The Committee will also discuss a revision FDA is considering to the Withdrawn or Removed List. Specifically, FDA is considering whether to amend § 216.24 to add an entry to the list:

hydroxyprogesterone caproate: all drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous birth. As previously explained in the Federal Register of July 2, 2014 (79 FR 37687 at 37689 through 37690), the list entry may specify that a drug may not be compounded in any form. Alternatively, the list entry may expressly exclude a particular formulation, indication, dosage form, or route of administration from an entry on the list, or a drug may be listed only with regard to certain formulations, indications, routes of administration, or dosage forms. FDA plans to seek the Committee's advice concerning the inclusion of this entry on the list.

The bulk drug substances to be discussed are separate topics and each topic is a particular matter involving specific parties.

Type, Nature, and Magnitude of the Financial Interests:

Dr. Gulur reported a financial interest in stock in a competing firm for the ibutamoren and ipamorelin topics. She holds shares of (b) (6) stock, valued between $25,000 and $50,000. (b) (6) is not an affected firm for the L-theanine, kisspeptin-10, and hydroxyprogesterone caproate topics.

In addition, Dr. Gulur reported that she holds stock in (b) (6) operates pharmacies that provide compounding services for drug products and could be financially affected by the discussions of the bulk drug substances at issue. The market value of the holdings in this security is between $25,000 to $50,000.

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. Gulur's financial interests in (b) (6) and (b) (6) exceed that amount, she has disqualifying financial interests.

Basis for Granting the Waiver:

Dr. Padma Gulur has unique qualifications and specialized expertise needed for these particular matters.

Dr. Padma Gulur is a standing voting member and Chairperson of the PCAC. She is a Professor of Anesthesiology and Population Health Sciences at Duke University, Executive Vice Chair of Duke Anesthesiology, and Director of Pain Management Strategy and Opioid Surveillance at Duke University Health Systems.

Dr. Gulur received her MBBS from Bangalore Medical College, Karnataka University. She completed her residency in anesthesiology at Boston Medical Center and fellowship in pain medicine at Massachusetts General Hospital. Dr. Gulur is board certified in anesthesiology and

pain medicine and specializes in advanced interventional pain management. She is a Fellow of the American Society of Anesthesiology and a member of several organizations including the International Neuromodulation Society, the International Association for the Study of Pain, the American Board of Anesthesiology, the American Society of Anesthesiologists and the North American Neuromodulation Society.

As a highly regarded physician and researcher, Dr. Gulur has authored numerous peer-reviewed publications on topics such as pain management in adult and pediatric patients, cancer-related pain, and opioid optimization. Additionally, Dr. Gulur has written several chapters in respected books on topics such as pediatric anesthesia, acute pain, trigeminal neuralgia, and rheumatic and arthritic disorders.

Dr. Gulur has developed a unique expertise in interpreting data and medical literature from her extensive clinical and research experience. Dr. Gulur has conducted studies and in-depth analyses on the pharmacology of pain assessment and management that addresses a variety of medications, and therapies, and utilizes a number of assessment tools. Her extensive research on pain management is published in numerous medical publications. Dr. Gulur's expertise will add valuable insight into discussions on whether the Agency should permit the use of these bulk drug substances in compounding by adding these substances to the 503A Bulks List and to the Withdrawn and Removed List. In addition, Dr. Gulur has extensive experience on the PCAC and as Chair of the PCAC, she provides valuable leadership and expertise at the meetings.

The particular matters are sensitive.

The topics are considered to be sensitive and the FDA Division responsible for review of bulk drug substances expects that the meeting is likely to receive significant public interest.

Dr. Gulur's expertise in these particular matters is necessary in the interest of public health.

One of the conditions that must be satisfied for a drug product to qualify for the exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 353a) is that the licensed pharmacist or licensed physician compounds the drug product using bulk drug substances (as defined in 21 CFR 207.3) that: (1) comply 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, are drug substances that are components of drugs 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, that appear on a list developed by the Secretary through regulations issued by the Secretary under section 503A(c) of the FD&C Act (the 503A Bulks List) (see section 503A(b)(1)(A)(i) of the FD&C Act).

Ibutamoren mesylate is the mesylate salt of a non-peptide small molecule that binds to and activates ghrelin receptors. Acting as a ghrelin receptor agonist, ibutamoren (the active moiety of the salt) can induce growth hormone release from the anterior pituitary gland in vitro and in vivo. Ibutamoren mesylate acts as a growth hormone secretagogue, a class of drugs that consists of a variety of synthetic peptide or non-peptide agents that stimulate endogenous GH release.

L-theanine is a non-proteinogenic amino acid present almost exclusively in the tea plant (Camellia sinensis). Oral L-theanine was determined to be Generally Recognized as Safe (GRAS) and is marketed in the United States as an ingredient in fruit juices and drinks, non-herbal teas, sports beverages, specialty bottled waters, chocolate bars and chews, hard candies, and breath mints, and chewing gum. L-theanine may be used as a dietary supplement, food, or drug product.

Ipamorelin (free base) is a pentapeptide hormone containing non-proteinogenic amino acids while Ipamorelin acetate is a salt form of a peptide consisting of five amino acids. Ipamorelin (free base) and ipamorelin acetate act as growth hormone secretagogues.

Kisspeptin-10 is a synthetic peptide consisting of ten amino acids. Kisspeptin is an upstream regulator of GnRH secretion. The pulsatile secretion of GnRH initiates puberty, coordinates ovulation, and maintains overall reproductive function.

One of the conditions that must be satisfied for the compounded drug 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.

Makena (hydroxyprogesterone caproate injection, 250 mg/mL), NDA 021945, was approved in 2011 under the accelerated approval pathway to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous birth. However, the postmarketing confirmatory trial failed to verify the clinical benefit of Makena and the available evidence demonstrated that Makena was no longer shown to be effective under its conditions of use. FDA concluded that the statutory standard in section 506(c) of the FD&C Act for expedited withdrawal was met, and that approval should be withdrawn. On April 6, 2023, the FDA Commissioner and Chief Scientist issued a decision withdrawing the approval of Makena and the ANDAs that referenced Makena.

Accordingly, in the interest of public health, it is important that the Agency has available the unique expertise in data interpretation and medical literature that Dr. Gulur will provide for the discussion of the particular matters before the Committee. Dr. Gulur's clinical and research experience will be necessary during the AC's discussion. Dr. Gulur's experience in assessing the pharmacokinetic properties of study treatments will add substantial value to discussions on pharmacokinetic data available to the committee. Additionally, Dr. Gulur's extensive research background evaluating the efficacy and safety of certain substances on children and adult subjects is essential expertise that will support discussions on whether ibutamoren mesylate, L-theanine, ipamorelin acetate ipamorelin (free base), and kisspeptin-10 provides clinically meaningful benefit in the intended patient population and whether the Agency should permit its use in compounding by adding it to the 503A Bulks List, as well as disussions regarding the Withdrawn and Removed List.

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

Dr. Gulur has developed a unique expertise in interpreting data and medical literature and will add valuable insight into discussions on whether the Agency should permit the use of these bulk drug substances in compounding by adding these substances to the 503A Bulks List and to the Withdrawn and Removed List. In addition, Dr. Gulur has extensive experience on the PCAC and as Chair of the PCAC, she provides valuable leadership and expertise at the meetings.

Dr. Gulur's holdings of both (b) (6) and (b) (6) each are less than 5% of her total stock holdings. (b) (6) Therefore, it is not anticipated that this meeting will substantially affect the stock price of either company, if it will affect it at all, or have a substantial effect on (b) (6) overall revenue.

Accordingly, I recommend that you grant Dr. Padma Gulur, a standing voting member and Chairperson of the Pharmacy Compounding Advisory Committee, a waiver from the conflict of interest prohibitions of 18 U.S.C. § 208(a).

Certification:

____X___ 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.

Emily C. Helms Williams -S

Digitally signed by Emily C. Helms Williams -S
Date: 2024.10.10 12:20:28 -04'00'

October 10, 2024

Emily Helms Williams
Director, Advisory Committee Oversight and Management Staff
Office of the Chief Scientist

Date