FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Topic 1

L-Theanine

Tuesday, October 29, 2024

8:00 a.m. to 9:39 a.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Takyiah Stevenson, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Voting)

Robin H. Bogner, PhD

Professor

University of Connecticut

School of Pharmacy

Department of Pharmaceutical Sciences

Storrs, Connecticut

Seemal R. Desai, MD, FAAD

(via video conferencing platform)

Founder and Medical Director

Innovative Dermatology

Plano, Texas

Clinical Assistant Professor

Department of Dermatology

University of Texas Southwestern Medical Center

Dallas, Texas

Padma Gulur, MD, FASA

(Chairperson)

Professor of Anesthesiology and Population Health

Executive Vice Chair

Department of Anesthesiology

Director of Pain Management Strategy and Opioid Surveillance

Duke University Health System

Duke University Medical Center

Durham, North Carolina

Kathleen M. Gura, PharmD, BCNSP, FASHP, FASPEN
Assistant Professor of Pediatrics
Harvard Medical School
Manager, Pharmacy Clinical Research Program
Boston Children's Hospital
Boston, Massachusetts

Elizabeth Rebello, RPh, MD, FASA, CPPS, CMQ
(via video conferencing platform)
Professor
Department of Anesthesiology and
Perioperative Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas

Brian Serumaga, PhD
(United States Pharmacopeia Representative)
Senior Manager, Personalized Medicines
United States Pharmacopeial Convention
Rockville, Maryland

Allen J. Vaida, BSc, PharmD, FASHP

Former Executive Vice President

Institute for Safe Medication Practices

Hatfield, Pennsylvania

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Thomas J. Lupton, PharmD, MBA, BCPS

(Industry Representative)

Director, Point-of-Care Pharmacy Services

On Demand Pharmaceuticals

Rockville, Maryland

Donnette D. Staas, PhD

(Industry Representative)

Vice President, Regulatory Strategy

Jazz Pharmaceuticals

Philadelphia, Pennsylvania

TEMPORARY MEMBERS (Voting)

Nancy Diazgranados, MD, MS, DFAPA

(L-theanine Topic Only)

Deputy Clinical Director

National Institute on Alcohol Abuse and Alcoholism

National Institutes of Health (NIH)

Bethesda, Maryland

Todd Durham, PhD

(Acting Consumer Representative)

Senior Vice President

Clinical and Outcomes Research

Foundation Fighting Blindness

Columbia, Maryland

Jonathan Emens, MD, FAASM, DFAPA

(L-theanine Topic Only)

Clinical Director of Mental Health & Chief of Psychiatry
Division of Mental Health
VA Portland Health Care System
Professor & Vice Chair, Department of Psychiatry
Oregon Health and Science University
Portland, Oregon

Eliot Katz, MD

(L-theanine Topic Only)

Division Chief, Sleep Medicine
Johns Hopkins All Children's Hospital
St. Petersburg, Florida
Los Angeles, California

Francis J. McMahon, MD

(L-theanine Topic Only)

Chief, Genetic Basis of Mood & Anxiety Section and Human Genetics Branch

National Institute of Mental Health Intramural Research Program, NIH

Bethesda, Maryland

Rita Weiss, PharmD, JD

(Acting National Association of Boards of Pharmacy Representative)

Clinical Pharmacist/Compliance

Trinity Health - PACE

Livonia, Michigan

FDA PARTICIPANTS (Non-Voting)

Frances Gail Bormel, RPh, JD

Director

Office of Compounding Quality and Compliance (OCQC)

Office of Compliance (OC), CDER, FDA

Ian F. Deveau, PhD

Deputy Director

OCQC, OC, CDER, FDA

Gabrielle Cosel, MSc

(via video conferencing platform)

Director

Division of Compounding Policy and Outreach (DCPO)

OCQC, OC, CDER, FDA

Charles Ganley, MD

Director

Office of Specialty Medicine (OSM)

Office of New Drugs (OND), CDER, FDA

Daiva Shetty, MD

Associate Director

Pharmacy Compounding Review Team (PCRT)

OSM, OND, CDER, FDA

Tracy Rupp, PharmD, MPH, BCPS, RD

Lead Consumer Safety Officer

OCQC, OC, CDER, FDA

Kemi Asante, PharmD, MPH, RAC

Lead Consumer Safety Officer

OCQC, OC, CDER, FDA

Russell Wesdyk, BS, MBA

Associate Director for Regulatory Affairs

Office of Product Quality Assessment II

Office of Pharmaceutical Quality

CDER, FDA

Marianne San Antonio, DO

(L-theanine Topic Only)

Physician

PCRT, OSM, OND, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(8:00 a.m.)

Call to Order

Introduction of Committee

DR. GULUR: Good morning, and welcome. I would first like to remind everyone to please mute your line when you are not speaking, and also a reminder to everyone to please silence your cell phones, smartphones, and any other devices if you have not already done so. For media and press, the FDA press contact is Amanda Hils. Her e-mail is currently displayed.

My name is Dr. Padma Gulur from Duke University, and I will be chairing today's meeting. I will now call the October 29, 2024 meeting of the Pharmacy Compounding Advisory Committee to order. We'll start by going around the table and introducing ourselves by stating our names and affiliations. Those participating in all five topic sessions of this meeting will introduce themselves first. Those participating in specific topics of this meeting will be introduced at the

start of their respective topic sessions. We will start with the FDA on my left, go around the table, and then address the virtual participants. Thank you.

DR. SAN ANTONIO: Marianne San Antonio, Pharmacy Compounding Review Team, FDA.

DR. SHETTY: Good morning. Daiva Shetty, Associate Director for Pharmacy Compounding Review Team and OND, FDA.

DR. GANLEY: Charlie Ganley. I'm Director of Office of Specialty Medicine in the Office of New Drugs.

DR. RUPP: Tracy Rupp, Team Lead, Office of Compounding Quality and Compliance, FDA.

CDR ASANTE: Commander Kemi Asante, Team Lead, OCQC, FDA.

MS. BORMEL: Gail Bormel, Director, Office of Compounding Quality and Compliance, FDA.

DR. WESDYK: Russ Wesdyk, ADRA, OPQA II, FDA.

DR. DURHAM: Todd Durham, Foundation Fighting Blindness.

DR. VAIDA: Allen Vaida, a pharmacist and retired from the Institute for Safe Medication Practices.

DR. STEVENSON: Takyiah Stevenson, Designated Federal Officer, FDA. And just a note for those that are participating in the L-theanine topic only, you'll be introduced at the start of that particular session.

DR. GURA: Kathleen Gura, Department of Pharmacy, Boston Children's Hospital.

DR. BOGNER: Robin Bogner, University of Connecticut School of Pharmacy.

DR. SERUMAGA: Brian Serumaga, Director of Personalized Medicines, United States Pharmacopeia.

DR. WEISS: Rita Weiss, NABP.

DR. DIAZGRANADOS: Nancy Diazgranados, NIAAA, NIH.

DR. STEVENSON: We'll continue to Dr. Lupton.

DR. LUPTON: Thomas Lupton, Director of Pharmacy Services, On Demand Pharmaceuticals.

DR. STAAS: Donnette Staas, Vice President,

Regulatory Strategy at Jazz Pharmaceuticals.

DR. STEVENSON: Now, we will have our virtual participants introduce themselves for the record.

Gabrielle Cosel?

DR. COSEL: Good morning. Gabrielle Cosel, the Director of the Division of Compounding Policy and Outreach in the Office of Compounding Quality and Compliance.

DR. STEVENSON: Dr. Rebello?

DR. REBELLO: Elizabeth Rebello, MD Anderson Cancer Center, Houston.

DR. STEVENSON: Dr. Desai?

DR. DESAI: Seemal Desai, board certified dermatologist from Dallas, Texas.

DR. STEVENSON: Thank you. I'll turn it back to the chair.

DR. GULUR: Thank you everyone, and welcome.

For topics such as those being discussed at this meeting, there are often a variety of opinions, some of which are very strongly held. Our goal is that this meeting will be a fair and

open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that advisory committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings; however, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

Today we will discuss the following bulk drug substances being considered for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with Section 503A

of the Federal Food, Drug, and Cosmetic Act, also known as the 503A Bulks List: ibutamoren mesylate; L-theanine; ipamorelin related bulk drug substances, ipamorelin acetate and ipamorelin free base; and kisspeptin-10. We note that the two nominations ipamorelin-related bulk drug substances have been withdrawn by the nominators, but FDA decided to evaluate these substances on its own initiative.

For each of the substances, we will hear presentations from the FDA, have the opportunity to ask clarifying questions, hold an open public hearing, and have committee discussion and voting. We have no nominators presenting today.

The September 18, 2024 Federal Register notice identified the uses FDA reviewed for each of the bulk drug substances being discussed at this meeting. These uses reflect those for which adequate support was provided in a nomination. In certain circumstances, FDA may also review substances in the context of unnominated or inadequately supported uses because, for example,

such uses appear to be widespread, are intended to treat serious conditions, or pose serious risks to patients.

In addition, nominations and FDA's evaluations for the bulk drug substances, which are included in the briefing documents posted on FDA's website, identify the proposed and reviewed uses, dosage forms, and routes of administration.

The committee will also discuss a revision FDA is considering to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness, the Withdrawn or Removed List. FDA now is considering whether to amend the rule to add one more 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. Thank you

Dr. Stevenson will read the Conflict of Interest Statement for this meeting's 503A Bulks List topics.

Conflict of Interest Statement

DR. STEVENSON: Thank you.

The Food and Drug Administration, FDA, is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception of the National Association of Boards of Pharmacy, NABP, United States Pharmacopeia, USP, and the industry representatives, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with federal ethics and conflict of interest laws, covered by but not limited to those found at 18 U.S.C. Section 208, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of this committee are in

compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs their potential financial conflict of interest, or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

Related to the discussion of today's meeting, members and temporary voting members of this committee have been screened for potential financial conflicts of interests of their own as well as those imputed to them, including those of their spouses or minor children and, for purposes of 18 U.S.C. Section 208, their employers. These interests may include investments; consulting; expert witness testimony; contracts, grants, CRADAs; teaching, speaking, writing; patents and

royalties; and primary employment.

During this session, the committee will discuss four bulk drug substances being considered for inclusion on the 503A Bulks List. FDA will discuss the following drug substances and the uses that FDA reviewed for each: 1) L-theanine for sleep disorders and anxiety disorders; 2) ibutamoren for treatment of growth hormone deficiency, GHD, osteoporosis, hip fracture, sarcopenia, obesity, and Alzheimer's disease; 3) ipamorelin acetate and ipamorelin free base for GHD and postoperative ileus; 4) kisspeptin-10 for the treatment of secondary hypogonadism in men. This is a particular matters meeting during which specific matters related to the four bulk drug substances will be discussed.

Based on the agenda for today's meeting and all financial interests reported by the committee and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Padma Gulur and Dr. Kathleen Gura.

Dr. Gulur is attending all topics. Her waiver involves stock holdings in a competing/ affected entity for all topics with an aggregate value between $25,000 and $50,000. Dr. Gulur's waiver also involves stock holdings in a competing firm for the ibutamoren and ipamorelin topics. The aggregate value of the stock is between $25,000 and $50,000.

Dr. Gura is attending all topics, and her waiver involves six stock holdings. The first stock holdings are in a competing/affected entity for all topics with an aggregate value between $25,000 and $50,000. The other five stock holdings are in competing firms: a competing firm for the L-theanine and kisspeptin topics; a competing firm for ibutamoren and ipamorelin topics; a competing firm for the L-theanine topic; a competing firm for the L-theanine, ibutamoren, and ipamorelin topics; and a competing firm for all topics. The aggregate value for each of the five stock holdings and competing firms is between $0 and $10,000.

The waivers allow these individuals to

participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website on the advisory committee meeting page, which can be found at www.fda.gov and by searching for October 29, 2024 PCAC. Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division at 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the bulk drug substances at issue.

We would like to note that Dr. Rita Weiss is a representative member from the National Association of Boards of Pharmacy, NABP, and Dr. Brian Serumaga is a representative member from the United States Pharmacopeia, USP. Section 102 of the Drug Quality and Security Act amended the

Federal Food, Drug, and Cosmetic Act with respect to the Advisory Committee on Compounding to include representatives from the NABP and the USP. Their role is to provide the committee with the points of view of the NABP and the USP. Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue; instead, they serve as the voice of the NABP and USP, entities with a financial or other stake in the particular matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Thomas Lupton and Dr. Donnette Staas are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Lupton is employed by On Demand Pharmaceuticals and Dr. Staas is employed by Jazz Pharmaceuticals.

We would like to remind members and temporary voting members that if the discussions involve any other bulk drug substances or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all participants to advise the committee of any financial relationships that they may have with the topics at issue.

Thank you, and I'll hand it back to the chairperson.

DR. GULUR: Thank you.

We will now proceed with FDA introductory remarks from Dr. Gail Bormel, immediately followed by an FDA presentation on investigational new drug and expanded access from Lori Bickel.

FDA Introductory Remarks - Gail Bormel

MS. BORMEL: Good morning, everyone. I'm Gail Bormel, Director of the Office of Compounding Quality and Compliance, the FDA office primarily responsible for developing and implementing

policies and compliance strategies addressing the quality of compounded drugs. I'd like to welcome you to the 12th meeting of the Pharmacy Compounding Advisory Committee.

As we've mentioned, we're going to be discussing today four bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding human drug products under Section 503A of the Federal Food, Drug, and Cosmetic Act. This list is known as the 503A Bulks List. As you've heard, the substances that will be discussed are ibutamoren mesylate; L-theanine, ipamorelin related bulk drug substances, including ipamorelin acetate and ipamorelin free base; and kisspeptin-10.

FDA is aware that some of these substances might be marketed in dietary supplements. The discussion today focuses on FDA's evaluation of these substances for the 503A Bulks List. Our discussion does not pertain to FDA's regulation of these substances as dietary supplements.

Section 503A of the FD&C Act addresses compounding

of drug products. Section 503A does not address dietary supplements.

We also note that whether a substance is marketed as a dietary supplement is not a criterion considered when evaluating a substance for inclusion on the 503A Bulks List, and including, or not including, a substance on the 503A Bulks List does not affect the availability of a substance in dietary supplements.

During this meeting today, we will also discuss whether to add an entry for certain drug products containing hydroxyprogesterone caproate to the list of drug products 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.

This list known as the Withdrawn or Remove List implements conditions under both Sections 503A and 503B of the FD&C Act. We have scheduled time for the nominators to speak before FDA's presentation and time for an open public hearing after FDA's presentation on each of the bulk drug

substances. There will also be an open public hearing after the FDA presentation for hydroxyprogesterone caproate.

I would also like to take this opportunity to provide you with an update on certain developments since the committee last met in June 2022. Since then, the agency has worked to establish and revise guidance with recommendations for compounders. In response to pressing drug shortages, we published guidance documents addressing the compounding of certain beta lactam products and the compounding of certain ibuprofen oral suspension products. Earlier this month, we published a guidance describing temporary policies for compounding certain parenteral drug products as a result of public health emergencies resulting from the consequence of Hurricane Helene.

We have also been working on policy documents for compounders under Section 503B of the FD&C Act, most notably involving the list of bulk drug substances for which there is a clinical need for use in compounding under Section 503B, which is

known as the 503B Bulks List and pertains to outsourcing facilities. Since June 2022, we have proposed to add two substances to the 503B Bulks List and propose that 13 substances not be added to the list at this time. FDA also added one bulk drug substance to the 503B list and determined that 12 bulk drug substances will not be added to the list.

We have also published a draft guidance concerning the prohibition on wholesaling under Section 503B of the FD&C Act and published revisions to draft guidances concerning the interim policy on compounding, using bulk drug substances under Sections 503A and 503B of the FD&C Act. In addition, we published a proposed rule to establish criteria for the list of drug products or categories of drug products that present demonstrable difficulties for compounding, known as the Demonstrable Difficulties for Compounding Lists, or DDC lists, under Sections 503A and 503B of the FD&C Act. Additionally, the agency proposed the first three categories of drug products for

both DDC lists.

We continue to issue compounding risk alerts to inform healthcare professionals, compounders, and consumers about risks associated with compounded drugs, including information on adverse events and product quality issues. Most recently, we issued an alert highlighting concerns with dosing errors associated with compounded semaglutide products. If you are not already receiving emails about our compounding risk alerts, you can sign up on the FDA human drug compounding website.

Additionally, the Compounding Quality Center of Excellence continues to engage with outsourcing facilities and other stakeholders to improve the quality of compounded drugs. We offer both instructor-led and self-guided trainings to support outsourcing facilities. We also have a free annual conference designed to give interested parties the opportunity to engage with FDA and learn about emerging trends and best practices to enhance the quality of compounded drugs. You can find all the

materials I discussed, plus many more, on FDA's compounding website.

We are glad you are here today to participate in the Pharmacy Compounding Advisory Committee. We have made some changes based on your feedback, including more time to review materials in advance of this meeting. We hope these changes improve your ability to contribute meaningfully, as your input and expertise are critical to the success of this process. We look forward to a productive meeting and to continuing to work together. Thank you again for joining us.

DR. GULUR: Thank you.

FDA Presentation - Lori Bickel

MS. BICKEL: Good morning, everyone. My name is Lori Bickel, and I'm a regulatory counsel in CDER's Office of New Drug Policy. Thank you for the opportunity to present this morning. I have no conflicts of interest to disclose.

Today, we're going to look at two ways investigational drugs and biological products can be used, either for research under an IND or for

treatment use under expanded access. The purpose of the discussion is to help inform the committee members and the public of ways in which an investigational drug can be studied or used to treat patients. First, I'll give an overview of the investigational new drug, or IND, submission requirements. This is needed before drugs can be studied in clinical trials. Then I'll move on to expanded access and how it differs from clinical trials. Finally, I'll take a quick look at some of the tools FDA has developed to help patients and physicians determine if expanded access is an appropriate option and to streamline the process if it's determined that it is.

We're going to be talking about ways to use investigational drugs and biological products. Research on investigational drugs is typically done under an IND. To get to an approved drug, clinical trials provide evidence of safety and effectiveness of the product. Clinical trials gather the information, which may lead to the product's eventual approval for commercial marketing and

widespread use.

Approval leads to the broadest availability for the product with full labeling for patients and potential third party reimbursement. However, if a clinical trial is not an option, then perhaps expanded access use may be an avenue for treatment use of an investigational product if appropriate conditions are met. Expanded access is really meant to be a last resort when other options are either exhausted or not available. I'd also like to note that both of these pathways are distinct from 503A and 503B compounding. Whether a product is or isn't being studied under an IND is not a consideration in determining whether a bulk drug substance is appropriate for inclusion on the 503A Bulks List.

We're going to start off with the IND for research or clinical trials; however, some of the key content in the IND submissions apply to both clinical trials and expanded access. When I think of the information submitted under an IND, I kind of break it into three categories.

The first is information about the investigator who will be conducting the study. This investigator may be a researcher within a large academic institution or it may be a practicing community physician. The basic information must be submitted about the investigator to make sure they are qualified to actually conduct the research. This is information about, again, their qualifications, their CV, and that is gathered on the forms that are listed on the slide.

The second bucket of information is information about the drug product to be studied: its chemistry; manufacturing; controls information, product identity, purity, strength; how it's distributed. In some cases, a Letter of Authorization, LOA, may be used to reference information about the drug that's already on file with FDA in an existing IND.

Continuing with information about the drug, we also need information about the safety and the efficacy of the product. Is it reasonably safe at

the dose and duration proposed? What clinical or nonclinical data does the sponsor have to justify these proposals in the protocol? As for efficacy, we need to know what is the sponsor's rationale to support the intended use of the drug in the investigation?

Now, the third set of information is information about the patient and the proposed treatment, the protocol for the investigation; that's the description of the disease or condition being studied. What are the eligibility criteria for the clinical trial? What clinical procedures and monitoring will be in place to evaluate the effect of the product and to minimize any risk to study participants? All INDs do need informed consent and IRB approval. Now, these key content slides don't capture everything, but hopefully they will give you an idea of the types of information FDA requires, and why, before a clinical study can begin.

Moving on to expanded access, in contrast to a clinical trial, which is use of an

investigational drug or biological product for research, expanded access is the use of an investigational drug or biological product to treat a patient. The patient must have a serious or immediately life-threatening disease or condition who does not have comparable or satisfactory alternative therapy. Expanded access really is meant to be the last resort.

The first thing I'm going to point out on this slide is the asterisk at the very bottom of it. The sponsor or manufacturer must agree to provide their product for expanded access treatment. FDA cannot force a sponsor to do that. However, once a sponsor agrees, there are three types of expanded access.

The first is individual or single patient. This may be in an emergency situation when treatment can begin immediately after the manufacturer or sponsor agreement to provide the product and after authorization is received from FDA, which often can be done over the phone. The second type is intermediate size, populations that

are typically more than one but generally smaller than the treatment IND protocol; however, there is no set number for intermediate size. The third type is treatment use, which is use by a larger or widespread population. This typically occurs after either compelling phase 2 or phase 3 data are available.

Moving on to the conditions that apply to all three types of expanded access, as I mentioned, the patient must have a serious or immediately life-threatening disease or condition. There must be no comparable or satisfactory alternative therapy available. It must not be an option to enroll a patient in a clinical trial. The potential benefits of the expanded access use must justify the potential risks, and the expanded access use must not interfere with or compromise the potential development of the expanded access use.

In 2009, FDA published our final rule on expanded access. In 2016, we released a question and answer guidance, which was revised in 2017. In

2022, an additional revised draft was published. FDA is in the process of reviewing public comments and finalizing another version of the Q&A guidance.

All research done under an IND, both clinical trials and expanded access, come with a full range of human subject protections. This slide includes the citations to the sections of the regulations that apply. Since the regs were published in 2009, FDA continues to assist interested parties to make sure that the Expanded Access Program is understood and the criteria are known and followed so the program is used appropriately and within its intended scope. These include a new form to simplify the single-patient IND submission process. It includes the updates to the guidances and FDA's website.

FDA also has an ongoing collaboration with the Reagan-Udall Foundation for the FDA, who has launched various tools to help with the process. Additionally, FDA's Oncology Center of Excellence launched Project Facilitate in 2019 to help provide one-on-one assistance through the expanded access

process.

This is a screenshot from FDA's website. It's designed to be user friendly with tabs for all various interested parties such as patients, physicians, industry, and IRBs. There's also a link to a series of FDA-produced informational videos. Here's contact information for any questions that either members of the committee or the public may have about the topics covered in my presentation today. Here are links to the regulations and guidances mentioned in the presentation. Thank you very much for the opportunity to present to you this morning.

DR. GULUR: Thank you.

Before we begin the L-theanine topic session, I would like our FDA member who has arrived more recently to introduce himself.

DR. DEVEAU: Good morning. I am Ian Deveau. I am the OCQC Deputy Director for Quality.

DR. GULUR: Thank you.

Panel members who will be in this topic will introduce themselves by stating their names and

affiliations. We will begin with Dr. Diazgranados.

DR. DIAZGRANADOS: I am Nancy Diazgranados. I'm the Deputy Clinical Director at NIAAA at NIH.

DR. GULUR: Thank you.

Dr. Emens?

DR. EMENS: Dr. Jonathan Emens, Oregon Health and Science University and VA Portland Health Care System.

DR. GULUR: Thank you.

Dr. Katz?

DR. KATZ: Hi. Dr. Eliot Katz. I'm the Director of the Sleep Center, Johns Hopkins All Children's Hospital Sleep Center.

DR. GULUR: Thank you.

Dr. McMahon?

DR. McMAHON: Francis McMahon, National Institute of Mental Health.

DR. GULUR: Thank you.

I would like to state into the record that we do not have a nominator presentation for the L-theanine topic. We will now proceed with the FDA presentation on L-theanine from Dr. Marianne

San Antonio.

FDA Topic 1 Presentation

Marianne San Antonio

DR. SAN ANTONIO: Good morning. My name is Marianne San Antonio, and I'm a physician in the Office of New Drugs. I will discuss the nomination for L-theanine for possible inclusion on the 503A Bulks List. I would like to recognize the entire evaluation team, as well as the contribution of many other FDA colleagues who helped with this evaluation, and special thanks to the Division of Psychiatry.

L-theanine was nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A of the FD&C Act. L-theanine was evaluated for sleep disorders and anxiety disorders. L-theanine products proposed in the nominations are: a sublingual 2.5 milligram tablet; a topical 10 percent cream; a subcutaneous or intramuscular injection with a 75-milligram vial and a 10-milligram per milliliter solution; and oral 50, 100, and 200-milligram capsules. We have

evaluated publicly available data on the physical and chemical characterization, historical use in compounding, and safety and effectiveness of this substance.

First, we will discuss L-theanine's physical and chemical characterization. L-theanine is a non-proteinogenic amino acid present in the tea plant. The molecular formula and molecular weight are shown here. L-theanine is available as a water soluble powder. An aqueous solution made from the powder must be stored at negative 20°Celsius for no more than 2 months.

There is no USP drug substance monograph for L-theanine. There is limited or no information for BDS characterization, including tests, limits, or results for impurities, which would allow FDA to assess the nature and level of individual impurities or total impurities in the nominated BDS. Endotoxin control is critical for injectable dosage forms. In conclusion, the nominated BDS, L-theanine, is not well characterized due to the lack of critical quality attribute controls.

Next, we will discuss L-theanine's historical use in compounding. L-theanine is marketed in the United States as an ingredient in oral dietary supplement products. FDA's literature search and outsourcing facility reports from 2017 to 2020 indicate that L-theanine has been compounded in the United States in oral formulations and as part of multiple ingredient injection solution products. Oral formulations have been advertised for use in sleep disorders and for managing symptoms of anxiety and stress. Clinical studies have evaluated the use of compounded formulations of L-theanine for age-related cognitive decline, ADHD, and sleep in pediatric subjects with ADHD.

In conclusion, L-theanine has been compounded in the United States since 2017. It has been marketed as oral and injectable formulations, but outsourcing facilities have not reported compounding products containing L-theanine since 2020.

Next, we will discuss L-theanine's

nonclinical safety. In pharmacological studies in rodents, L-theanine prolonged sleep, decreased anxiety-like behavior, reduced depression-like behavior, and improved memory; however, the mechanisms underlying the pharmacological effects of L-theanine are poorly understood. In rats, L-theanine is quickly absorbed following oral administration with plasma concentrations peaking 30 minutes after dosing.

L-theanine distributes well to all tissues, including the brain, the liver, and the kidney. In fasted rats, L-theanine delivered orally is metabolized to glutamic acid and ethylamine, which are eliminated in urine. Age and health status appear to affect the pharmacokinetics of L-theanine in rodents.

In adult rats given L-theanine in their diet for 13 weeks, the oral NOAEL was 4,000 milligrams per kilogram per day. Using body surface area, the oral NOAEL translates to a human equivalent dose of 640 milligrams per kilogram that provides safety margins of about 96.8 times in adults and

48.8 times in children, for the highest oral dose of 400 milligrams used in most clinical studies. Although dietary consumption of L-theanine seems to be well tolerated, no information is available to compare systemic exposure from dietary consumption to once-daily treatment at the same total dose.

Nonclinical reproductive and developmental toxicity studies of L-theanine delivered orally were not identified at the time of this evaluation. The nominators did not submit, and FDA did not identify, nonclinical toxicity studies of L-theanine delivered via the nominated sublingual, topical, subcutaneous, or intramuscular routes of administration. In conclusion, nonclinical safety information are too limited to inform safety considerations for the inclusion of L-theanine in the 503A Bulks List.

Now, we will discuss L-theanine's clinical safety. We were not able to find pharmacokinetic data for children or for sublingual, topical, subcutaneous, or intramuscular routes of administration in humans. A search of the FAERS

database for reports of adverse events retrieved 3 cases associated with L-theanine. Various adverse events were reported such as diabetic ketoacidosis, balance disorder, and feeling abnormal; however, the assessment of these cases was limited because they were confounded by multiple other ingredients.

CFSAN collects reports of adverse events involving food, cosmetics, and dietary supplements. A search of CFSAN retrieved 4 cases that listed L-theanine as the only active ingredient in the suspect product. Adverse events reported were allergic type reactions; increased anxiety; attention disturbance; nausea and diarrhea. Reported adverse events in adults with medical conditions who received oral L-theanine were agitation, sedation, increased duration of sleep, vivid dreams, headache; exacerbations in OCD requiring inpatient admission; appetite loss, nausea, vomiting, diarrhea, constipation, reflux; tachycardia, fatigue; neutropenia; and elevated CRP.

In studies of pediatric subjects with medical conditions, subjects received oral and sublingual L-theanine, and one adverse event, a new facial tic, was reported. In these studies, it is not known whether the reported adverse events were due to L-theanine or due to other concomitant medications. In conclusion, oral and sublingual administration of L-theanine appear to be generally well tolerated, but there were no studies in which subjects received L-theanine via the topical, intramuscular, or subcutaneous routes of administration.

Next, we will discuss the evidence regarding effectiveness for the two nominated uses: sleep disorders and anxiety disorders. Sleep disorders encompass several different disorders that affect different parts of the normal sleep cycle. The sleep disorders considered in this evaluation are listed here. Lyon et al. 2011 was submitted by the nominator. In this double-blind, placebo-controlled trial, boys with ADHD were randomized to receive 6 weeks of either oral

L-theanine or placebo.

The purpose of the study was to investigate improvements on objective and subjective measures of sleep quality. Actigraphy is an activity-based sleep monitor that employs the use of a wristwatch-like recording device worn during sleep to measure movement. The study authors reported that participants in the L-theanine study arm had increased sleep efficiency and fewer bouts of nocturnal activity; however, there was no difference between treatment groups in sleep latency, which is the time to fall asleep, or sleep duration, which is the total sleep time, and PSQ data did not correlate with the actigraphy data.

Study limitations include baseline measures on actigraphy, PSQ, and core ADHD symptoms were not reported. The authors did not discuss which type of stimulants, which are medications for ADHD that are known to adversely affect sleep, the subjects were taking and when these were being given. The authors did not show results by subgroup to discuss whether being on a stimulant had an effect on the

study outcomes. Compliance with wearing the actigraph watch was not reported.

Although the authors report slight changes in some actigraphy measures in this small study that examines sleep quality in boys with ADHD, they did not achieve the prespecified statistical level of significance, and it is unclear whether these changes are clinically meaningful. Because no female subjects with ADHD were included, it is unclear whether these results are generalizable to a larger population of children with ADHD and sleep disorders. Because it is unclear if any of the study participants had a primary sleep disorder, it is unclear if the study findings can be generalized to populations with primary sleep disorders who do not have ADHD.

FDA identified two additional studies that discussed the use of L-theanine in adults with poor sleep quality. Thiagarajah et al. 2022 was a randomized study in which adults with poor sleep quality received 4 weeks of either RLX2 or placebo. RLX2 is a substance containing alpha-S1 casein

tryptic hydrolysate and L-theanine. The authors report that sleep duration and sleep habitual efficiency were improved in the RLX2 group versus placebo.

Ota et al. 2015 was an 8-week, open-label study in 17 adults with schizophrenia and 22 age and sex matched healthy subjects. L-theanine was added to the subjects' current treatment for schizophrenia. The authors reported that L-theanine ameliorated positive symptoms of schizophrenia and improved sleep quality. Study limitations for these two studies include small sample size, absence of the use of objective measures to assess these outcomes. The authors do not report whether any of the study subjects had a primary sleep disorder.

L-theanine was given with another substance as part of the intervention in both studies, and it is unknown if study subjects were taking other medications that may have affected their sleep. Subjects had other underlying comorbidities or medical conditions; therefore, it's difficult to

determine the contribution of L-theanine to the study outcomes, and it's unclear whether study results would be generalizable to a larger population of patients with primary sleep disorders.

In conclusion, there's insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of sleep disorders. There were no studies in which subjects received L-theanine via the sublingual, topical, intramuscular, or subcutaneous routes of administration. Professional society guidelines do not discuss the use of L-theanine for sleep disorders, and there are FDA-approved therapies with established efficacy for many sleep disorders.

Anxiety disorders include disorders that share features of excessive fear and anxiety. Anxiety disorders differ from one another in the types of objects or situations that induce fear, anxiety, or avoidance behavior. Anxiety disorders differ from developmentally normative fear or anxiety by being excessive or persisting beyond

developmentally appropriate periods. They differ from transient fear or anxiety by being persistent and typically last 6 months or more. The anxiety disorders considered in this evaluation are listed here.

FDA identified one study in which L-theanine was evaluated in subjects with a primary anxiety disorder. Sarris et al. 2019, a phase 2, randomized, double-blind, placebo-controlled, 8-week pilot study, enrolled 46 adults with generalized anxiety disorder who were non-responsive to their current medication and evaluated anxiety and insomnia outcomes. In addition to their current medications, study subjects received L-theanine 450 milligrams per day or a placebo for the first 4 weeks of the study.

Participants who did not have a reduction in anxiety at week 4 were titrated to 900 milligrams L-theanine per day or a matching placebo for the remaining 4 weeks of the treatment. Some subjects in both the L-theanine group and the placebo group also received psychotherapy. The authors report

that for both, anxiety and insomnia outcomes, no difference between L-theanine and placebo groups was observed.

FDA identified several other studies which evaluated the use of L-theanine in subjects who had symptoms of anxiety. Rizzo et al. 2022 was an open-label study without placebo in 34 children with Tourette syndrome, or chronic tic disorder, associated with anxiety symptoms. Subjects were randomized to receive either psychoeducation or L-theanine and vitamin B6 daily for 2 months. The authors report that there was no difference in mean anxiety scores between treatment groups.

Hidese et al. 2017 was an open-label study without placebo in 20 adults with major depressive disorder. Subjects received L-theanine orally for 8 weeks. Authors reported improvement in anxiety symptoms following administration of L-theanine. Ross et al 2021 was a case report without placebo of an adult with PTSD and bipolar II disorder with generalized anxiety symptoms who received 13 medications and dietary supplements, including

L-theanine, for 3 months. The subject reported improvement in mood and anxiety at the end of the study.

These studies were limited by small sample size and lack of blinding and placebo control. The use of concomitant medications during the intervention confounds interpretation of the intervention, making it difficult to determine the contribution of L-theanine to study outcomes. It is unclear whether study results would be generalizable to a larger population of patients with primary anxiety disorders.

In conclusion, there is insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of anxiety disorders. There were no studies in which subjects received L-theanine via the other nominated routes of administration. Professional society guidelines do not discuss the use of L-theanine for anxiety disorders, and there are FDA-approved therapies with established efficacy for many anxiety disorders.

In summary, for physical and chemical characterization, L-theanine is not well characterized due to the lack of critical quality attribute controls such as impurities and endotoxins for compounding proposed dosage forms. For historical use in compounding, although L-theanine has been used in pharmacy compounding in the United States since at least 2017, outsourcing facilities have not reported compounding drug products containing L-theanine since 2020. It has been marketed as compounded oral and injectable formulations for various conditions.

For nonclinical safety, the nominators did not submit, and FDA did not identify, nonclinical toxicity studies of L-theanine delivered via the nominated sublingual, topical, subcutaneous, or intramuscular route of administration. Nonclinical studies identified at the time of this evaluation were too limited to inform safety considerations for the inclusion of L-theanine in the 503A Bulks List.

For clinical safety, although oral and

sublingual administration of L-theanine appears to be generally well tolerated, there were no studies in which subjects received L-theanine via the topical, intramuscular, or subcutaneous route of administration. For effectiveness, there is insufficient information concerning effectiveness to support use of oral L-theanine for the treatment of sleep disorders and anxiety disorders. There were no studies on L-theanine via the other nominated routes of administration for the nominated uses. Professional society guidelines do not discuss the use of L-theanine for either sleep disorders or anxiety disorders, and there are FDA-approved therapies with established efficacy for many sleep disorders and anxiety disorders.

After considering the information currently available, a balancing of the four evaluation criteria weighs against L-theanine being added to the 503A Bulks List. Thank you. This concludes my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions to the presenters. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the presenters?

Dr. Desai, virtually presenting, would you state your name and ask your question?

DR. DESAI: Yes. Thank you very much, Dr. Gulur. This is Dr. Seemal Desai, board certified dermatologist, Innovative Dermatology in Dallas, Texas, and President of the American Academy of Dermatology. My question was specifically just to double check on the other routes of administration.

Was there any data at all regarding topical uses and percutaneous absorption of L-theanine?

DR. SAN ANTONIO: This is Marianne San Antonio with the FDA. Thank you for your question. No, we were unable to find any studies that examined the use of L-theanine via topical routes of administration.

DR. DESAI: Thank you very much, and I appreciate you mentioning that in the slide. I just wanted to clarify on the absorption. Thank you very much.

DR. GULUR: Any other questions? Yes?

DR. EMENS: Yes. Jon Emens. I just wanted to clarify, for the Lyon et al. 2011 study -- that was the study in boys with ADHD -- I don't know if this is in your presentation, but it was in your materials. They did a really interesting adjustment for multiple comparisons, where they chose an alpha that they wanted to go with. So to clarify, there wasn't a standard procedure done for adjusting for multiple comparisons, and they didn't state how many comparisons they did in that study;

is that correct?

DR. SAN ANTONIO: Marianne San Antonio, FDA. Thank you for your question. Yes, that's correct. It appears from the way they described their analytical plan that they initially had planned an alpha of 0.01, and when it was not reached, they reported out alphas of less than 0.05, but they didn't give any more explanation of it than that.

DR. GULUR: Thank you.

Any other questions?

(No response.)

Open Public Hearing

DR. GULUR: We will now begin the open public hearing session.

Both the FDA and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the

open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the product, and if known, its direct competitors. For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this

open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and respect.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

We have one open public hearing.

Speaker number 1, please state your name and any organization you are representing for the record. You have 15 minutes.

DR. ROSEBUSH: Sure. My name is Lee Rosebush. I am actually here to represent on behalf of a coalition of pharmacies, including FarmaKeio, pharmacies on the 503A statute compound with L-theanine. In addition to myself, I'm joined by Jim LaValle, the chair of the International Peptide Society, and gets paid as an educator for

the International Peptide Society, as well as consulting with a variety of compounding pharmacies.

I'll go ahead and start the presentation, if we can go to our first slide. Also, to address the question that was asked related to topical, specifically, uses of L-theanine, I would point out a March 2018 article explicitly titled, Topical Delivery of L-Theanine Eliminates GPA Induced Acute Skin Inflammation via Downregulating Endothelial PECAM-1 and Neutrophil Infiltration and Activation. And inside of that, in the abstract, it does say that topical delivery of L-theanine possesses anti-inflammatory effects on acute skin inflammation, as well as other uses. So there is, in fact, studies on the use of this in a topical setting.

Now, to go ahead and get started, I'd like to start out with a little bit of a paradox associated with L-theanine because I do think that the record here needs to demonstrate, in fact, the actual history associated with L-theanine. As FDA

stated, there is not a USP drug monograph. What I would say in that perspective is that is a little bit misleading in the fact that there is, in fact, a USP monograph as a dietary supplement monograph associated with that.

In addition, in this perspective, FDA by itself has recognized GRAS status for both synthetic production, as well as non-synthetic production under the conditions of use of up to 250 milligrams of L-theanine per serving. So there are, in fact, GRNs that recognize this substance, and FDA has said they are, in fact, safe to use in the oral route for up to 250 milligrams.

On top of that, there is no limitation as to how many times somebody could take those products, and FDA has recognized that in that perspective. So if I as a consumer wanted to walk into the gas station and buy L-theanine, I could do so. But yet, this is supposed to be about patient safety, and to say that a pharmacist can't compound with that same product that they could buy in a vending machine at a gas station, recommended by somebody

who's not a healthcare provider, and they could take that multiple times per day.

In addition, under the current regulatory framework, it's important to remember not only could a gas station sell L-theanine in this perspective, a GNC could sell this, and sell it multiple times.

And let's get this one step closer to the compounding pharmacy. In fact, a pharmacy today can sell L-theanine as a vitamin in its pharmacy and, in fact, the pharmacist itself could walk up and recommend to a patient, who walked in, to take L-theanine for sleep efficacy, which the FDA has recognized in the studies that it just mentioned for quality of sleep, which do show some benefit in this perspective, and sell that to a patient, an unlimited amount. But yet, if a patient walks into their doctor, who is going to monitor them and get a prescription for L-theanine under FDA's recommendation, that is not ok because that is unsafe.

So that same pharmacist can recommend I take

L-theanine, but that same pharmacist cannot compound L-theanine under the supervision of a physician because that's too dangerous. I want to make sure that comes across from this perspective.

So what the FDA's action would do today, if the PCAC were to follow them, is to remove the ability to compound with L-theanine. It would not eliminate L-theanine because I could walk into the Chevron across the street and buy all the L-theanine I want. All it would do is reduce the ability for those that may be allergic to something in L-theanine to get it compounded without that product or to get a different dose, and it would eliminate their ability to get that. So in fact, it makes it more dangerous by removing this, in this perspective, and that is the conundrum in the paradox of this one.

I also would point out, if we can go to our next slide, that there are four specific criteria that are supposed to be reviewed and used during the review of these substances. The first, is the substance well characterized physically and

chemically? 2) Has the substance been used historically in compounding? 3) Are there concerns about whether a substance is effective for a particular use? And 4) Are there concerns about the safety of substance abuse in compounding?

If we go through this very quickly, which we will see at the end, one, FDA has a GRN for these substances, both synthetic and non-synthetic, for the production. FDA has recognized underneath number 3 they've made a big deal about subcutaneous and IM injection issues, and endotoxin. Notice they left out the oral part, which their slides explicitly say oral and sublingual is well tolerated.

FDA has said in this perspective that underneath their materials, it is considered GRAS, generally recognized as safe; 4) if you look at the three studies that they just mentioned on sleep efficacy, all three of them mention that there was efficacy for sleep in this perspective for sleep quality; and then 2) we're going to show you that, historically, we have talked to just 9 pharmacies,

and those 9 pharmacies have dispensed over 70,000 prescriptions, and that material has been submitted to the administrative record here, and the 70,000 prescriptions using FDA's own data from FAERS and CAERS shows that there has been less than 10 total side effects, adverse events, that have been reported to them. And I can tell you from the 70,000 that we received, it was zero serious unexpected adverse events.

It's also important to remember that the FDA in this perspective comes from their authority to review these substances under 21 CFR 216.23. Specifically, these are those four requirements. It's important to recognize when it talks about a substance versus when it talks about a product in this situation. In this situation, we've been talking about the safety and physical chemical characteristics of L-theanine, for example, endotoxin testing.

We can simply point to ICH guidance documents and FDA's own guidance documents to ensure that endotoxin testing has been done

properly. The same thing with aggregates and other situations and impurities that you'll see later on, FDA completely ignores the ICH guidance, as well as their own guidance documents in how these testings could be done moving forward.

In addition, to its own Federal Register notice -- I want to make sure that this gets on the record -- these are quotes directly from the 2019 FDA guidance, their Federal Register notice for 21 CFR 216.23, quote, "Through the rulemaking process, FDA received feedback that any party believes it is not adequately considered the GRAS determination of a substance in a particular case, FDA will consider that feedback before finalizing its proposal to include or not include a substance on the 503A Bulks List."

Today I'm making that formal request, and it will we submitted in that perspective to the agency that this GRAS determination, especially for oral uses of this product, is considered before moving forward.

2) Quote, "A substance that is safe when

used as a food may not be safe as an active ingredient in a drug product, for example, with other routes of administration other than oral." In other words, FDA in their own Federal Register notice said that when oral is considered, and there is a GRAS, safety and the physical and chemical characteristics in that perspective are a given, period.

3) "The existence of alternative therapies is not one of the four criteria FDA is using to evaluate nominatable drug substances, nor is the availability of approved alternatives dispositive when considering whether to add a substance to a list." In other words, if there's another substance that has been approved for this, it is not supposed to be what is considered. There is nowhere in any of these requirements that this is supposed to be a superiority or inferiority comparison. That is not done for FDA-approved products, nor should that be done for this. And if you look up those four requirements, and this is why that slide is there, nowhere do you see a

comparative aspect of this. Nowhere do you see a superiority analysis in the situation.

Finally, "We consider the existence of an FDA-approved or OTC monograph drug product relevant to FDA's consideration of the safety criterion to the extent there may be therapies that have been demonstrated to be safe under the conditions of use set forth in the approved labeling, and the effectiveness criteria to the extent that there may be alternative therapies that have been demonstrated to be effective for certain conditions." Again, according to FDA's own in this perspective, if it has been considered safe for GRAS purposes, it should be considered safe for this, especially for oral and sublingual uses.

So it all should be noted in this situation that FDA is arbitrarily picking and leaving itself open for comparative and, in this this perspective, potential action, when safety and efficacy standards should apply for inclusion on this list.

In 21 CFR 216.23(d), FDA states that the substances added to the list, to date, to the 503A

Bulks List, are, quote, "Based on evidence currently available, there are, quote, 'inadequate data to demonstrate the safety or efficacy of any drug product compounded using any of the drug substances listed in paragraph A of this section.'" In other words, FDA is saying that those substances that they have previously reviewed didn't have the adequate data, but yet they included those. Here, they're saying it doesn't have the adequate data, and yet they want to deny it. That is the definition of arbitrarily picking when a standard applies and when it doesn't apply.

Now, as you've heard, there are four criteria. We have tried to make it very quick for you before I turn it over to my colleague here to talk about the actual substance itself. FDA's own GSRS and NIH's own PubChem have a detailed listing for L-theanine. It is perfectly positive and able to be done; do a test to see a way to determine the drug in and of itself.

The product's a commonly used dietary supplement. As I mentioned, it is literally sold

millions of times per year, and we have over 70,000 prescriptions on record. We've also provided COAs in the written materials that show endotoxin testing, purity testing, et cetera, that are based on FDA's own ICH guidance documents and testing guidance for these materials, and they are in the written materials we have submitted.

FDA's GRAS determination should be considered, and there's USP dietary supplement monographs as well for identification purposes. We have provided real-world evidence from pharmacies that have dispensed over 76,000 prescriptions involving L-theanine. L-theanine has been used over 76,000 times, that's dispensed at a prescription perspective, and we've shown that it is effective. In fact, FDA's own FAERS study show that doses up to 900 milligrams were positive in this perspective and well tolerated. These substances here were nominated for 50, 100, and 200. That's 16 times less the dose that was studied for safety purposes.

Are there concerns about the safety of the

substances used for compounding? Our real-world evidence and retrospective analysis have found that with over 76,000 prescriptions, we are not aware of any reported adverse events related to L-theanine containing dispensed compounded prescriptions. The FDA's own review of the FAERS and CAERS data have shown only four adverse events reported for L-theanine alone, that's total, and they were non-life threatening. We conducted an additional search of the FAERS and CAERS database to bring the data current and found no additional reports.

So as we mentioned, the issues that they've raised for endotoxin, it really relates to the API issues here, not the compounding concerns associated with those. If that really is the concern, make a guidance document with the ICH testing on endotoxin, et cetera, going down a list for 503A in these substances. It's not the right to be able to remove these in this perspective for access to these patients. We've provided the GSRS, as well as PubChem limitations, and there are links there.

These, so that way you can see in the written evidence, there are, in fact, GRAS for synthetically produced and non-synthetically produced. These are the ICH guidances, specifically and FDA's own guidances, that are used for COA purposes for testing for endotoxin. From this perspective, these testings can be done. In addition, orally in this perspective should be considered for the dosing.

Has the substance been used historically in compounding? I'm going to turn it over to Jim here.

DR. GULUR: I would like to advise you that you have both registered as one open public hearing speaker, and it is a combined 15 minutes. There's 2 minutes and 20 seconds left.

MR. LaVALLE: Thank you for the remaining time.

Real-world evidence, the clinical evidence about the usage of potential benefits or risks of a medical product is derived from the analysis of real-world data. If we look, 13 examples of

real-world evidence reviewed the insights of how real-world evidence has been used to support regulatory submissions and resulting feedback from FDA.

Let's get to a couple of studies here. Current uses for theanine: anti-anxiety or decrease stress response; neuroprotection; reducing excitotoxicity, glutamate antagonist; promotes relaxation without drowsiness; sleep issues, not a sedative but promoter of anxiolysis; and then improved focus, cognitive enhancement.

This is Suntheanine, a proprietary extract of theanine. It's a 98 percent theanine extract, no indication of adverse reactions or contraindications, and reported to be safe based on favorable tox studies. It is GRAS, as mentioned before. Several studies reported anti-anxiety effect. This is a 2019 randomized, double-blind, placebo-controlled trial with 30 major psychiatric illnesses; 200 milligrams of theanine versus placebo for 4 weeks; cognitive tests assessments, sleep latency disturbances improved significantly

on theanine. Conclusion of the author, theanine has the potential to promote mental health in the general population with stress-related ailments and cognitive impairments.

Another randomized, placebo-controlled trial crossover study at the National Institute of Mental Health and National Center for Neurology and Psychiatry in Japan. Ingestion of 200 milligrams of L-theanine by men for obstructive sleep apnea 1 hour before bed and did improve sleep quality, and also decreasing both dream recall and nightmares, and no significant adverse effects noted.

A 2024 double-blind, randomized, placebo-controlled trial on 30 adults 18 to 65; 400 milligrams of theanine daily or placebo. L-theanine group demonstrated decreased time asleep after 28 days and significantly reduced light sleep after 14 and 28 days. L-theanine group had significant improvement in the Stroop test reaction at 14 and 28 days; placebo, no improvement after 28 days. Conclusion is on the next page, and I'll

finish with this.

L-theanine supplementation administered for 28 days, safe; no side effects reported; significantly decreased perceived stress; significantly decreased perceived stress and light sleep; improved sleep quality and enhanced cognitive attention in the studied population. I believe that is my time. Thank you.

DR. GULUR: Thank you.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

Yes, Dr. Bormel?

MS. BORMEL: I would like to be recognized to just respond a little bit to what was said.

DR. GULUR: Yes.

MS. BORMEL: Thank you. Gail Bormel, OCQC Compliance Director. In the beginning, I mentioned that we are not here to opine on dietary supplements. We don't regulate dietary supplements, and what we discussed today won't affect the the sale of dietary supplements. But

our job is very different today. It's to opine on its use as a drug. That's what we're being asked to do today. We have tens of thousands of pharmacies that can compound drugs with a patchwork of state regulations. We are the FDA with our federal law, and we evaluate things as drugs to be compounded and dispensed by pharmacies. This is a different paradigm.

Not only was L-theanine nominated for oral use and topical use, but it was also nominated for subcutaneous IM injections, and those are very different entities. And I'd like to point out that the USP monograph for dietary supplements is not the same as an applicable USP monograph that we would consider for drug use. There are different testing standards in the USP dietary supplement monograph than we would expect in a USP drug monograph, applicable monograph.

In addition, there were discussions about adverse event reporting and the lack of serious adverse effects with L-theanine. Please be aware that there is no mandatory adverse event reporting

for drugs under Section 503A of the Act. Once something is compounded as a drug under 503A, we may or may not ever find out about any adverse events. So there's no standard for the reporting of adverse events to the agency, period. In addition, my understanding is we haven't received the COA that was mentioned or the testing that was mentioned in the OPH, so just wanted to make the committee aware of that as well because we would have passed that along.

DR. GULUR: Thank you.

(Pause.)

Clarifying Questions from the Committee (con't)

DR. GULUR: If we could just wait, we're going to get into the clarifying questions, remarks, and then allow everyone to have an opportunity to comment. We do have some more time, and since we do, we will now take the remaining time for clarifying questions.

When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if

you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the FDA at this time, or remarks from the FDA?

Yes, we recognize.

DR. DEVEAU: Thank you. Again, I am Ian Deveau. I am the Deputy Director within the Office of Compounding Quality and Compliance. I'm the Deputy Director for Quality. Regarding the USP and the USP standard for L-theanine, it is listed within the USP as a dietary ingredient. There are a few things I should point out.

The manufacture of L-theanine is done in accordance with GMPs for dietary ingredients and supplements. There is no requirement nor consideration for the quality of water used in such manufacture; therefore, it's not generally

considered controlled for the level of endotoxin, and, again, there is no requirement under the dietary ingredient GMPs.

Furthermore, there are a number of differences between a USP drug ingredient monograph and a USP dietary ingredient monograph. I will point out one difference. From the standpoint of a dietary ingredient, USP's microbial limits are 1 to 2 orders of magnitude greater than it is for a drug substance within the USP, so it may have a higher level of microbial contaminants. So this is, again, just to emphasize they are not equivalent. They're not the same.

DR. GULUR: Thank you.

Yes?

DR. GANLEY: Yes. Hi. This is Charlie Ganley. I just want to make some comments regarded to the reference to real-world evidence. Real-world evidence is the clinical evidence about the usage and potential --

DR. GULUR: Would you mind bringing the microphone closer to yourself?

DR. GANLEY: Sorry about that.

So it's the clinical evidence about the usage and potential benefits or risk of a medical product derived from analysis of real-world data. Various sources of real-world data can be analyzed in non-interventional studies, including registries, electronic health records, and medical claims. The information provided in the presentation are simply numbers of prescriptions filled by unidentified pharmacies over an unknown period of time. It does not identify the use, dose, route of administration, and duration of exposure, information that we would have in real-world evidence. Most importantly, it does not provide any data related to the safety, and most importantly, the effectiveness of the drug. So simply providing the numbers of prescriptions is not sufficient.

DR. GULUR: Thank you.

Do any members of the committee have questions for the FDA?

(No response.)

DR. GULUR: I do have a few clarifying questions for the FDA. Would you, for the benefit of the committee, help us understand the GRAS, G-R-A-S, if you could relate what that is and how that is applicable based on the OPH testimony we just heard.

MS. BORMEL: Could you please repeat the question?

DR. GULUR: The GRAS that the OPH speakers spoke to, if you could help the committee understand how that applies in this setting.

DR. DEVEAU: I'm not quite sure if I understood the question, but I will respond anyway, and if I get it wrong, please feel free to correct me. A GRAS status is for a food, dietary ingredients, not as a drug.

DR. GULUR: So just to confirm, having GRAS status does not mean it is something that can be used to compound drugs.

DR. DEVEAU: Certainly, not by itself.

DR. GULUR: Thank you.

There was also a question posed in the open

public hearing of topical use, that there is a study for skin inflammation. I'm assuming that we did not have skin inflammation as one of the criteria for this. Is that one of the reasons it was not discussed?

DR. ALBUQUERQUE: Hi. This is Edna Albuquerque. I'm one of the nonclinical reviewers supporting compounding. There is a study conducted in mice. It's a study in which L-theanine was applied to the ear of mice that received tPA topically to induce inflammation. It is a study specifically designed to address mechanisms by which L-theanine might have anti-inflammatory effects.

That study does provide some pharmacological information about mechanisms involving inhibition of interleukins and inhibition of other mechanistic pathways that might contribute to anti-inflammatory activity; however, that study does not address absorption of L-theanine applied topically. It does not inform the safety of L-theanine, and it can't be used in terms of understanding to which

extent L-theanine applied topically would reach the systemic circulation. So I hope that helps.

DR. GULUR: Thank you.

Any questions?

(No response.)

DR. GULUR: Anything virtual?

(No response.)

MS. BORMEL: Can I just add --

DR. GULUR: Yes.

MS. BORMEL: -- just to answer your question, Dr. Gulur -- this is Gail Bormel, FDA -- the study that was just discussed is not for the uses that were reviewed by the agency, which we heard earlier.

Committee Discussion and Vote

DR. GULUR: Thank you for the clarification. I wanted to make sure that we understood that correctly; that that was not an indication that this presentation was directed towards.

Seeing that there are no questions from the rest of the committee or our virtual members, the committee will now turn its attention to address

the task at hand, the careful consideration of the data before the committee, as well as the public.

We will now proceed with questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

We will proceed with our first question, which is a voting question. We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote. Please press the button firmly that corresponds to your vote. If you are unsure of your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the

screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

For question 1, FDA is proposing that L-theanine not be included on the 503A Bulks List. Should L-theanine be placed on the list? If you vote no, you are recommending FDA not place the bulk drug substance on the 503A Bulks List. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or national formulary, monograph, or a component of an FDA-approved drug.

You may vote now.

DR. VAIDA: The yes agrees with this?

DR. GULUR: So I'll read it again.

If you vote no, you are recommending FDA not

place the bulk drug substance on the 503A Bulks List, which is the FDA recommendation at this time. If the substance is not on the list, then obviously it won't be compounded.

Was that clear for the rest of the committee as well? Yes will place it on the bulks drugs list, and no will not.

Are we all comfortable with our votes?

(No audible response.)

DR. GULUR: We will have a little bit of a lag, as our virtual members will be voting by mail, so thank you for your patience.

(Voting.)

DR. STEVENSON: Takyiah Stevenson, DFO. For the record, there are 2 yeses, 11 noes, and zero abstentions. Thank you.

DR. GULUR: So at this time, we will go around the table, and each of the members who have voted will state their name and their vote for the record, and if they would like, the reason for their vote. We'll start at the end of the table with the first voting member.

DR. McMAHON: Francis McMahon, NIMH. I voted no because I wasn't persuaded that L-theanine was safe or effective for the proposed usages.

DR. KATZ: Eliot Katz. I voted no.

DR. EMENS: Jonathan Emens. I voted no. With regards to safety, I, again, wasn't necessarily convinced there. We used adaptive servo-ventilation in patients with heart failure and sleep apnea for a long time before we realized, at least for certain types of devices, we were actually increasing mortality, so anecdotal reports of safety don't carry a lot of weight with me.

I think the other piece is just around efficacy. I think if the argument is it's going to be used as a drug, presumably it's going to be used for sleep disorders and psychiatric disorders, and there, there's not really good data at all on efficacy. The studies there were not very good. I certainly can't speak for the American Academy of Sleep Medicine, but I have worked to write practice parameters for the ASM, and the data that was presented would not allow it to meet criteria for

recommendation for use for any sleep disorder. And as the FDA noted in their presentation, it hasn't been approved by any professional societies for treatment of any psychiatric or sleep disorders, so that is the reason for my vote.

DR. DIAZGRANADOS: Nancy Diazgranados. I voted no. I think any report of 76,000 prescriptions with no adverse events is not data that I can consider real.

DR. WEISS: Rita Weiss with the National Association of Boards of Pharmacy. I voted no.

DR. SERUMAGA: Brian Serumaga with the USP. I voted no. Although there is a dietary supplement monograph for this, there is no USP-NF monograph, so I voted no.

DR. BOGNER: Robin Bogner. I voted yes. L-theanine is a small molecule for which compounders can evaluate the API quality based on a certificate of analysis and reject a vendor, or accept, or ask for more information. It has been shown to have a high safety margin, at least the nonclinical data, and there's at least some

evidence of efficacy in some patients. And since compounding is meant for individual patients, I voted yes.

DR. GURA: Kathleen Gura, Boston Children's Hospital. I voted no. There's simply inadequate evidence to support its use as a drug, and the lack of certificate of analysis to even review is disturbing.

DR. VAIDA: Yes. I really voted no. I'm sorry I pressed the wrong button, but I --

DR. GULUR: That's not a problem. Just to clarify for that, by the way, if you do feel like you have pressed the wrong button, until the vote is closed, you do have the ability to change it.

DR. VAIDA: But I really voted no because I didn't believe the efficacy of it, and also the other way that they want to do the ingredients.

DR. GULUR: Would you mind restating your name and your vote one more time?

DR. VAIDA: Allen Vaida. No.

DR. GULUR: Thank you.

DR. DURHAM: Todd Durham. I voted no.

DR. GULUR: Dr. Desai, would you like to read out your vote?

DR. DESAI: Yes. Seemal Desai. I voted no. Thank you.

DR. GULUR: Dr. Rebello?

DR. REBELLO: Elizabeth Rebello, MD Anderson Cancer Center. I voted no based on the lack of adequate safety and efficacy data, and the lack of USP monograph.

DR. GULUR: Thank you.

I'm Padma Gulur, and I voted no for reasons that have already been stated. In addition, when something is available for compounding as a drug, even if it is for an individual patient, as the open public hearing speaker said, usually patients go for compounding because they are allergic to either some substance that's available in the products outside or for different dosages. And while there is some safety data, nonclinical safety data, that says that we have some room with the amount and the dosages, it does leave it open for compounding at dosages that have not been studied.

So the lack of that safety and efficacy data, in addition to other reasons, is the reason I voted no. Thank you.

Now that the vote is complete, we will move on. This is the end of the L-theanine discussion. Thank you, everyone.

Adjournment

DR. GULUR: We will now take a quick 10-minute break. Panel members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will reconvene at 9:50 for the next topic. Thank you.

(Whereupon, at 9:39 a.m., the topic 1 session was adjourned.)

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Topic 2

Ibutamoren Mesylate

Tuesday, October 29, 2024

9:50 a.m. to 10:55 a.m.

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Takyiah Stevenson, PharmD

Division of Advisory Committee and

Consultant Management

Office of Executive Programs, CDER, FDA

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Voting)

Robin H. Bogner, PhD

Professor

University of Connecticut

School of Pharmacy

Department of Pharmaceutical Sciences

Storrs, Connecticut

Seemal R. Desai, MD, FAAD

(via video conferencing platform)

Founder and Medical Director

Innovative Dermatology

Plano, Texas

Clinical Assistant Professor

Department of Dermatology

University of Texas Southwestern Medical Center

Dallas, Texas

Padma Gulur, MD, FASA

(Chairperson)

Professor of Anesthesiology and Population Health

Executive Vice Chair

Department of Anesthesiology

Director of Pain Management Strategy and Opioid Surveillance

Duke University Health System

Duke University Medical Center

Durham, North Carolina

Kathleen M. Gura, PharmD, BCNSP, FASHP, FASPEN
Assistant Professor of Pediatrics
Harvard Medical School
Manager, Pharmacy Clinical Research Program
Boston Children's Hospital
Boston, Massachusetts

Elizabeth Rebello, RPh, MD, FASA, CPPS, CMQ
(via video conferencing platform)
Professor
Department of Anesthesiology and
Perioperative Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas

Brian Serumaga, PhD
(United States Pharmacopeia Representative)
Senior Manager, Personalized Medicines
United States Pharmacopeial Convention
Rockville, Maryland

Allen J. Vaida, BSc, PharmD, FASHP

Former Executive Vice President

Institute for Safe Medication Practices

Hatfield, Pennsylvania

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Thomas J. Lupton, PharmD, MBA, BCPS

(Industry Representative)

Director, Point-of-Care Pharmacy Services

On Demand Pharmaceuticals

Rockville, Maryland

Donnette D. Staas, PhD

(Industry Representative)

Vice President, Regulatory Strategy

Jazz Pharmaceuticals

Philadelphia, Pennsylvania

TEMPORARY MEMBERS (Voting)

Charles Billington, MD

(Ibutamoren Mesylate Topic Only)

Chief, Section of Endocrinology and Metabolism

Minneapolis Veterans Affairs (VA) Health Care System Minneapolis, Minnesota

Todd Durham, PhD

(Acting Consumer Representative)

Senior Vice President

Clinical and Outcomes Research

Foundation Fighting Blindness

Columbia, Maryland

Connie B. Newman, MD, MACP

(Ibutamoren Mesylate Topic Only)

Adjunct Professor

Department of Medicine

Division of Endocrinology, Diabetes and Metabolism

New York University Grossman School of Medicine

New York, New York

Thomas J. Weber, MD

(Ibutamoren Mesylate Topic Only)

Professor of Medicine

Division of Endocrinology, Metabolism and Nutrition

Duke University Medical Center

Durham, North Carolina

Rita Weiss, PharmD, JD

(Acting National Association of Boards of Pharmacy Representative)

Clinical Pharmacist/Compliance

Trinity Health - PACE

Livonia, Michigan

Jack A. Yanovski, MD, PhD

(via video conferencing platform; Ibutamoren and Ipamorelin topics only)

Chief, Section on Growth and Obesity

Associate Scientific Director for

Translational Medicine

Division of Intramural Research, Eunice Kennedy

Shriver National Institute of Child Health and

Human Development, NIH

Bethesda, Maryland

FDA PARTICIPANTS (Non-Voting)

Frances Gail Bormel, RPh, JD

Director

Office of Compounding Quality and Compliance (OCQC)

Office of Compliance (OC), CDER, FDA

Ian F. Deveau, PhD

Deputy Director

OCQC, OC, CDER, FDA

Gabrielle Cosel, MSc

(via video conferencing platform)

Director

Division of Compounding Policy and Outreach (DCPO)

OCQC, OC, CDER, FDA

Charles Ganley, MD

Director

Office of Specialty Medicine (OSM)

Office of New Drugs (OND), CDER, FDA

Daiva Shetty, MD

Associate Director

Pharmacy Compounding Review Team (PCRT)

OSM, OND, CDER, FDA

Tracy Rupp, PharmD, MPH, BCPS, RD

Lead Consumer Safety Officer

OCQC, OC, CDER, FDA

Kemi Asante, PharmD, MPH, RAC

Lead Consumer Safety Officer

OCQC, OC, CDER, FDA

Russell Wesdyk, BS, MBA

Associate Director for Regulatory Affairs

Office of Product Quality Assessment II

Office of Pharmaceutical Quality

CDER, FDA

Madeline Wolfert, MD

(Ibutamoren Mesylate Topic Only)

Physician

PCRT, OSM, OND, CDER, FDA

C O N T E N T S

P R O C E E D I N G S

(9:50 a.m.)

Call to Order

Introduction of Committee

DR. GULUR: Thank you, everyone.

Before we begin the ibutamoren mesylate topic session, panel members who will be in this topic will introduce themselves by stating their names and affiliations. We will begin with Dr. Billington.

DR. BILLINGTON: Good morning. Dr. Charles Billington from the Minneapolis VA Medical Center and the University of Minnesota.

DR. GULUR: Thank you.

Dr. Cooke?

DR. COOKE: I'm David Cooke. I'm the Clinical Co-Director of Pediatric Endocrinology at Johns Hopkins.

DR. GULUR: Dr. Newman?

DR. NEWMAN: Good morning. I'm Dr. Connie Newman. I'm at New York University School of Medicine. I'm in the Department of Medicine in the

Division of Endocrinology on Diabetes and Metabolism.

DR. GULUR: Dr. Weber?

DR. WEBER: Hi. My name is Tom Weber. I'm an adult endocrinologist at Duke University Medical Center in Durham, North Carolina.

DR. GULUR: Dr. Yanovski?

DR. YANOVSKI: Hi. Jack Yanovski, Chief of the Section on Growth and Obesity at the National Institute of Child Health and Human Development Intramural Program. I'm a pediatric endocrinologist.

DR. GULUR: Thank you.

I would like to state into the record that we do not have a nominator presentation for the ibutamoren mesylate topic. We will now proceed with the FDA presentation from Dr. Madeline Wolford.

FDA Topic 2 Presentation

Madeline Wolfert

DR. WOLFERT: Good morning. My name is Madeline Wolfert. I'm a physician with the

Pharmacy Compounding Review Team in the Office of New Drugs, and I will be presenting ibutamoren mesylate. I would like to recognize the evaluation team, as well as the contribution of many other FDA colleagues. Our special thanks to the Division of General Endocrinology in OND.

Ibutamoren mesylate was nominated for inclusion on the 503A Bulks List. It is also known as MK-677 and LUM-201. These terms will be used interchangeably. The proposed dosage forms are oral capsules or tablets, 10 and 25 milligrams. We refer to the oral route unless otherwise noted. Uses evaluated were growth hormone deficiency, GHD; osteoporosis; hip fracture; sarcopenia; obesity; and Alzheimer's disease, AD. We consider the criteria: physical and chemical characterization; historical use and compounding; available evidence of effectiveness or lack of effectiveness; and safety.

Ibutamoren mesylate is a small molecule. It has no USP monograph. It can be synthesized from commercially available starting material. It is

stable at minus 20 degrees for 4 years in powder form. It is soluble in water and ethanol. Certificates of analysis include ID and a purity test, but not chiral purity, drug substance related impurities, or residual solvents. The likely impurity profile would be specific to and determined by the synthetic route used. Because the COAs do not include limits or results for impurities, it's impossible to know the nature and level of impurities.

In conclusion, ibutamoren mesylate is not well characterized because certain critical characterization data relating to chiral purity, drug substance related impurities, or residual solvents were not found.

Here's what we found on historical use and compounding. It was first synthesized in 1995 to identify an orally active growth hormone secretagogue, GHS. It's been studied for conditions including GHD; obesity; hip fracture; osteoporosis; and AD. None of the studies appear to have utilized a compounded formulation.

The substance is marketed online to reverse aging and is a supplement in bodybuilding in various dosage forms. It's unclear if any pharmacies are compounding such products. It's not recognized in the European or Japanese pharmacopeias. In conclusion, the extent to which ibutamoren mesylate has been historically used in compounding is unclear. Currently available data are too limited to inform historical use for compounding.

Now, I'll discuss pharmacology and PK information. Based on nonclinical data, ibutamoren mesylate finds and activates ghrelin receptors. It can induce growth hormone, or GH, released from the pituitary gland. It can also trigger hypothalamic release of GHRH that can stimulate GH release from somatotrophs. A single IV or oral dose increases GH levels in animals; however, following treatment of rats for 6 weeks, it was unable to increase GH levels. Loss of increased GH following continuous treatment may be due to increased expression of somatostatin or receptor internalization and

desensitization.

Based on nonclinical information, oral bioavailability is greater than 60 percent. It is metabolized via CYP450 and glucuronidation. Limited clinical PK information shows high oral bioavailability and long duration of action of 24 hours.

I'll now provide a brief overview of GHD, which is inadequate secretion of GH from the pituitary. It can be congenital or acquired. Some cases have no known cause, or idiopathic, and may be childhood or adult onset. It can be complete or partial. Diagnosis is based on signs and symptoms and GH stimulation tests. A random GH level is not useful because levels fluctuate throughout the day. IGF-1 levels are helpful in screening, but alone are not reliable for diagnosis. Signs and symptoms include those seen on this slide.

There are multiple recombinant human GH preparations approved for children and adults. In pediatric patients, GH is used to normalize growth velocity and adult height and is titrated based on

growth response. IGF-1 levels monitor adherence and safety. In adults, GH offers benefits in body composition, exercise capacity, and quality of life. GH is titrated according to clinical response, side effects, and IGF-1. Ibutamoren mesylate, a GHS, has been studied for GHD; however, because it activates ghrelin receptors in the pituitary and hypothalamus, some residual endogenous GH secretion must be preserved; that is, partial and not complete GHD.

I'll now present studies on effectiveness for GHD. Chapman 1996 studied 32 healthy adults. Results showed ibutamoren mesylate enhanced GH secretion and increased IGF-1. Chapman 1997 studied 9 adults with GHD with ibutamoren mesylate for two 4-day periods. Authors found IGF-1 and GH increased from baseline. Study limitations are short duration, small sample size, and endpoints did not evaluate therapeutic effect.

Codner studied 18 children with idiopathic GHD. Authors found short-term administration increased GH, IGF-1, and IGFBP-3 in some children.

Authors noted that subsequent studies would be required to address whether prolonged treatment can sustain increases in GH and IGF-1 and increase growth velocity. Study limitations are short duration, small sample size, and lack of clinically meaningful endpoints.

Bright studied data from 68 children with GHD who received ibutamoren mesylate, placebo, or rhGH. Authors found height velocity on ibutamoren doses was 6 to 6.9 cm per year versus placebo 4.5 and rhGH 11.1. The authors noted that higher baseline peak GH and IGF-1 levels were positive predictive enrichment markers for increased height velocity on ibutamoren. Note that this is retrospective analysis of data.

Moving to osteoporosis, it's a disease where bone mineral density and bone mass decrease. Diagnosis involves clinical history, signs and symptoms, and measuring BMD. Treatment includes nutrition and exercise and various approved medications as listed on the slide.

Murphy studied postmenopausal women with

osteoporosis with alendronate and ibutamoren mesylate, alone and in combination, and placebo. Markers of bone formation and resorption increased with ibutamoren and decreased with alendronate. This reduction was mitigated with the combination of ibutamoren and alendronate. BMD increased at the femoral neck by 4.2 percent with the combination group versus 2.5 percent alendronate alone, but similar enhancement was not seen at other sites versus alendronate alone. Ibutamoren alone did not increase BMD versus placebo. IGF-1 increased 40 percent with ibutamoren. Authors concluded that the anabolic effect of ibutamoren mesylate attenuated the suppressive effect of alendronate on bone formation but did not translate into increases in BMD other than the femoral neck. Although the femoral neck is an important site for fracture prevention, lack of enhancement in bone mass at other sites compared with alendronate alone is a concern when weighed against potential side effects of enhanced GH secretion.

Moving to hip fractures, these often occur

in patients greater than 65 years old. Treatment is usually a combination of prompt surgical repair, rehabilitation, and medication for pain, blood clots, and infection. Successful long-term management of patients is challenging. Rapid muscle loss may impact effective rehab and recovery.

Bach studied subjects recovering from hip fracture with ibutamoren mesylate or placebo. Both groups showed improvement over time with no differences in functional performance measures, FPMs. Ibutamoren showed trends for greater improvement in some FPMs and ability to live independently. IGF-1 increased in the ibutamoren group greater than placebo. Authors concluded that although ibutamoren mesylate increased IGF-1, it was uncertain whether clinically significant effects on physical function were achieved.

Adunsky studied patients recovering from hip fracture and found that IGF-1 increased with ibutamoren mesylate but was not paralleled by improvement in most FPMs. The study was terminated

early due to a safety signal of congestive heart failure. The authors concluded that the AEs in a relatively small patient population makes it likely that the risk-benefit for this indication is not acceptable.

Now to sarcopenia, it is the age-associated loss of skeletal muscle function and mass. It likely has a multifactorial etiology. Symptoms may include strength and functional decline that contribute to adverse outcomes. There are no approved drugs for sarcopenia. Current interventions focus on activity and nutrition.

Of note, studies were not conducted in subjects with sarcopenia. A trial in 104 adults with strength deficits found IGF-1 increased in a dose-dependent manner after 2 weeks, and 24-hour GH levels increased with ibutamoren mesylate. Murphy studied 8 healthy males with diet-induced protein catabolism. Ibutamoren mesylate for 7 days reversed nitrogen wasting with less weight loss. Authors noted that future studies should determine whether these anabolic effects would persist with

prolonged treatment and if they will be associated with clinical benefit. A proof-of-concept study in 71 healthy adults found that ibutamoren mesylate increased 24-hour mean GH and fat-free mass over 12 months, although increased FFM did not result in changes in strength or function.

Next, obesity, this is a chronic condition that increases risk for heart disease, diabetes, and cancer. Diagnosis is based on medical history and high BMI. Treatment may involve the various FDA-approved options as listed on this slide. Svensson studied 24 males with obesity and found that ibutamoren mesylate increased GH, IGF-1, and FFM with no change in body fat. Authors noted that further studies need to evaluate whether a higher dose or prolonged treatment can promote a reduction in body fat.

Lastly, Alzheimer's disease, a progressive disease that affects memory, thinking, and behavior. Specific causes are not fully understood but likely involve a combination of factors. Symptoms include memory loss and cognitive

impairment that progresses. Treatment depends on the stage of disease. There are medications approved for different stages and to treat symptoms associated with AD.

A 2008 study evaluated disease progression in subjects with mild to moderate AD. Efficacy measures were changed from baseline at month 12 on various clinical instruments listed on this slide. Authors found that ibutamoren mesylate increased IGF-1 but found no significant differences between treatment groups on efficacy measures. Authors concluded that despite noting a robust increase in IGF-1, ibutamoren mesylate was ineffective at slowing the rate of progression of AD.

To conclude, there is insufficient information to support effectiveness of ibutamoren mesylate for the evaluated uses. Most of the available data have limitations such as lack of demonstration of clinically meaningful therapeutic effects, small study sizes, and short duration. These uses have the potential to be serious, and there are currently FDA-approved drugs with

established efficacy for GHD, osteoporosis, obesity, and AD, and alternative treatment methods for hip fracture and sarcopenia.

We will now switch gears to discuss safety. In rats, ibutamoren mesylate and other ghrelin agonists induce hypotension. Ghrelin receptors are expressed in the brain reward system, and ghrelin has been shown to induce responses typically evoked by drugs of abuse. By activating ghrelin receptors, ibutamoren mesylate could stimulate reward processing and potentially induce reinforcing in addictive behaviors; however, nonclinical studies were lacking to demonstrate whether it has reinforcing or addictive properties.

Acute toxicity, repeat-dose toxicity, genotoxicity, or carcinogenicity studies were not found in public literature. Developmental and reproductive toxicity studies with ibutamoren mesylate were also not found; however, treatment of mice with ghrelin resulted in negative effects on fertilization, implantation, and embryofetal development.

In conclusion, for nonclinical, the desired response of increased GH may be lost during continuous treatment with ibutamoren mesylate. It can induce hypotension in rats. Via activation of ghrelin receptors, it may have reinforcing properties. The finding of developmental toxicity with a ghrelin receptor agonist raises safety concerns.

For clinical safety, we considered these sources. A FAERS search retrieved reports of vomiting and abdominal pain, inability to feel a finger, and intracranial infarct in a man with underlying medical conditions on concomitant medications. A CAERS search retrieved additional reports that included weight loss; diarrhea; headache; decreased activity; and mood alteration. For published case reports, AEs included hepatomegaly, elevated liver enzymes, dyslipidemia, hyperglycemia, and elevated HbA1c. Our ability to interpret these reports is limited by insufficient case details and concomitant medications.

In terms of clinical trials, there were

three studies in patients with GHD treated with ibutamoren mesylate for 4 days to 6 months. AEs included increased appetite; vomiting; diarrhea; headache, night sweats; and increased transaminases, white blood cell count, and creatinine.

A study treated women with osteoporosis with alendronate and ibutamoren mesylate individually and in combination. GH-mediated AEs were noted in ibutamoren groups, such as weight gain; edema; abdominal distension; carpal tunnel syndrome. Subjects discontinued with ibutamoren for reasons including headache; night sweats; hip/leg pain; abdominal pain; hyperprolactinemia; transaminase elevation; hyperglycemia; hypertension; fluid retention; heartburn; and rash.

For hip fracture, there were two studies. In Bach, there were reports of thrombosis and deaths. These were reported as non-drug related. The ibutamoren mesylate group had increases in glucose, insulin, and HbA1c, as well as more reports of edema and fluid overload. In the second

trial, it is very important to note that the study was terminated early due to a safety signal of CHF, four in the ibutamoren mesylate arm versus one in placebo arm. AEs which may be mechanism based include CHF and increase blood pressure. AEs with higher frequency with ibutamoren mesylate were elevated glucose and HbA1c, myalgia, and arthralgia. The author stated that MK-677 has an unfavorable safety profile in hip fracture patients.

A study in males with obesity reported a transient increase in prolactin and cortisol. There was impairment of glucose homeostasis. Drug-related AEs include increased glucose, transient increase in ALT and AST, and gastritis and sweating. For Alzheimer's disease, one study found that the incidence of AEs, serious AEs, and serious drug-related AEs were comparable between ibutamoren mesylate and placebo. Deaths were considered non-drug related. There were more drug-related laboratory AEs with ibutamoren, driven by increased glucose and HbA1c.

Finally, there were five studies of ibutamoren mesylate, 2 to 50 milligrams, from 1 week to 2 years. Three studies in healthy adults and adults with functional impairment found AEs of increased appetite; lower extremity edema; abdominal pain; muscle pain; carpal tunnel syndrome; and discontinuations due to lightheadedness, and shortness of breath, and warm sensation. Increased fasting glucose, cortisol, and HbA1c were reported. One study noted that increased glucose correlated with BMI, which per author suggested that ibutamoren mesylate may result in impaired glucose tolerance with predisposing risk factors. The dose was down-titrated in some subjects due to increased glucose or joint pain. AEs with no causality assessment provided were cancers and MI. A study in older adults with strength deficits reported increased fasting glucose. A study with diet-induced protein catabolism reported increased fasting glucose, stomach ache, and dizziness.

In summary, ibutamoren mesylate was

evaluated in adults and children with GHD, adults with obesity, and older adults with strength deficits, functional impairment, osteoporosis, hip fracture, and AD. Various doses have been studied with durations up to 2 years. Serious AEs included CHF; thrombosis; cancer; and MI. AEs leading to discontinuation included hyperglycemia; hyperprolactinemia; increased transaminases; hypertension; fluid retention; headache; night sweats; abdominal pain; heartburn; rash; lightheadedness; shortness of breath; and warm sensation. Other common AEs include increased HbA1c and insulin, musculoskeletal complaints, and increased appetite.

For additional safety information, there are known potential risks associated with elevated GH and IGF-1. Warnings and precautions in FDA-approved rhGH labeling include increased risk of neoplasm, glucose intolerance, intracranial hypertension, fluid retention, and others as listed on this slide. We note that AEs associated with rhGH were reported with ibutamoren mesylate such as

hyperglycemia and fluid retention. And finally, older adults with high IGF-1 are at increased risk for incident disease such as dementia, vascular disease and osteoporosis, or death. Higher IGF-1 is associated with cancer risk across ages. There is a lack of safety data on ibutamoren mesylate and its risks associated with higher IGF-1.

To conclude, serious safety concerns include CHF; hyperglycemia; elevated liver enzymes; edema; and fluid overload. Other AEs include musculoskeletal pain, increased appetite, and hyperprolactinemia. It stimulates production of endogenous GH, which stimulates IGF-1. There are known potential risks associated with drug products that increase IGF-1. There is a lack of safety data on ibutamoren mesylate and the risks associated with higher IGF-1, in particular, for the proposed uses in older adults. There are currently available therapies for the treatment of adults with GHD and growth failure due to GHD in children, osteoporosis, obesity, and AD.

On balance, the physicochemical

characterization, limited information on historical use, lack of evidence of effectiveness, and specific safety concerns identified for ibutamoren mesylate way against inclusion. In particular, ibutamoren mesylate is not well characterized, there are potential serious safety risks associated with its use, and there is limited evidence of benefit with its use for the nominated conditions, which are serious. These are concerning given availability of FDA-approved products indicated to treat many of these uses.

After considering the information currently available, a balancing of the criteria weighs against ibutamoren mesylate being added to the 503A Bulks List. Thank you very much. This concludes my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions for the FDA presenter. When acknowledged, please remember to state your name for the record before you speak, and direct your question to a specific

presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible. Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up questions with, "That is all for my questions," so we can move on to the next panel member.

Are there any clarifying questions for the FDA presenter?

Yes?

DR. COOKE: You pointed out that there was a lack of data on the chirality of the compounded substance. Is there data from either the preclinical or clinical studies that point to either the chirality of the drugs used in those studies or the importance of chirality for response?

DR. WOLFERT: This is Dr. Wolfert. Thank you for your question. I understand you're asking about any preclinical or clinical information about the chirality of the drug. I can refer this question to my colleagues in pharm-tox. Thank you.

DR. ALBUQUERQUE: Thank you. This is Edna Albuquerque, one of the nonclinical reviewers supporting the Compounding Pharmaceutical Review Team. We don't have any data in the literature that would talk about the extent to which one chiral form would be more or less potent than another, so we would not have information to address your question from the literature.

DR. COOKE: Then, a second question, the preclinical data seemed to show pretty clear tachyphylaxis in rats. The human studies extended out to 2 years, and I didn't see anything that suggested, even from just IGF-1 levels, that there's a drop-off in the impact of this. Is there a difference between the drug delivery between the preclinical studies and the human studies, or some explanation for why there might be that difference in tachyphylaxis?

DR. WOLFERT: This is Dr. Wolfert. Thank you for your question. I understand you're asking about the potential drop-off in IGF levels over time that was seen in nonclinical studies. In

clinical studies, there were a few examples of a potential slowing of effect. Svensson et al. 1998, that was conducted in men with obesity, observed that GH levels increased with MK-677 throughout the 8-week period.

Although the GH response was lower at 2 and 8 weeks compared to the initial response, authors theorized a possible negative feedback from IGF-1 on GH secretion. Murphy et al. 2001 also showed a slight attenuation of the increase in IGF-1 over the 12-month experimental period, but I think more data is probably needed. Thank you.

DR. COOKE: Thank you.

DR. GULUR: Yes? Please remember to state your name again.

DR. BILLINGTON: Dr. Billington.

Dr. Wolfert, ghrelin was briefly famous after its discovery as the hunger hormone due to its engagement in appetite-related receptors to the brain in the hypothalamus, at the time thought, and that would suggest that one potential outcome would be increased appetite and weight gain. The Nass

study that you cited, in addition to showing increased lean body mass, showed increased weight and increased adiposity after stimulation with ibutamoren. My question is, was there any more of that, that you ran across, any other indications of appetite stimulation or weight gain?

DR. WOLFERT: Yes. This is Dr. Wolfert. Thank you for your question. I understand you're asking about potential weight gains in clinical studies. The Svensson 1998 article that did evaluate patients with obesity actually did show a weight gain of 2.7 kg at 8 weeks of MK-677 treatment, with a p of less than 0.01 versus placebo. Authors attributed this to the anabolic effect of fat-free mass in the treatment group with a maximum increase of 3 kilograms measured by DEXA scan, corresponding to the increase in body weight of this cohort.

In addition, increased appetite was also recognized as a potential adverse event in multiple clinical studies. In patients with pediatric growth hormone deficiency, the authors theorized

that this could be a result of catch-up growth.

DR. BILLINGTON: Thank you. I think that's it.

DR. GULUR: Thank you.

Any other clarifying questions for the FDA presenters; anything virtual?

(No response.)

Open Public Hearing

DR. GULUR: Since we have completed the clarifying questions for the FDA presenter, we will now begin the open public hearing session.

Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decision making. To ensure such transparency at the open public hearing session of the advisory committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you

may have with the product, and if known, its direct competitors. For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at this meeting. Likewise, FDA encourages you, at the beginning of your statement, to advise the committee if you do not have any such financial relationships. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them. That said, in many instances and for many topics, there will be a variety of opinions. One of our goals for today is for this open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy, and

respect.

For those presenting virtually, please remember to unmute and turn on your camera when your OPH number is called. For those presenting in person, please step up to the podium when your OPH number is called. As a reminder, please speak only when recognized by the chairperson. Thank you for your cooperation.

Speaker number 1, please state your name and any organization you are representing for the record. You have 15 minutes.

DR. ROSEBUSH: Sure. My name is Lee Rosebush. As I mentioned before, I am a PharmD, RPh, JD. I'm here to represent a coalition of pharmacies, including FarmaKeio, who specifically compound ibutamoren. Before I get started, I'd like to be able to address a couple of things for the administrative record, particularly with the last product, L-theanine, because I wasn't able to address.

One, we heard at least one vote that was made a no because COAs weren't provided. The COAs

that are referenced in FDA's presentation are not our COAs. In fact, we provided additional written COAs --

DR. GULUR: May I remind you to please address the topic at hand.

DR. ROSEBUSH: I will. I say that because it applies to all four substances. It begs into question whether or not our materials that were supplied and written materials were actually reviewed.

Two, from this perspective, we heard multiple votes from the PCAC members that said they were rejected because there was no USP monograph. If there was a USP monograph for this product, we wouldn't be here because we'd legally have the right to compound this product. Two, as the USP person on this panel can verify, I have went to USP, met with him, as well as the leadership of USP, and asked to make a monograph for this product -- hence, my disclosure here -- including all four of these products, and was told I could not make a USP monograph for these because they're

not FDA-approved products, even though we have the material to do so.

So the fact that multiple votes were said no, and that we can move forward here with anything that are going to be noes without a USP monograph, shows that this is an impossible standard to make, and one, again, that will have to be legally challenged because we have asked for a USP monograph to be made; one cannot be made. And if the vote will be no because there is no USP monograph moving forward, it's an impossible standard to meet. Hence, that applies to this substance, as well as all of the substances, including L-theanine, where the votes have already occurred.

Again, as we've discussed previously, there are four factors that should be considered moving forward for review: is the substance well characterized physically and chemically? Has the substance been used historically in compounding? Are there concerns about whether a substance is effective for a particular use? And are there

concerns about the safety of the substance for use in compounding?

This is specifically the regulation. I would include all of the comments and the quotes that I read from the last, the L-theanine, specifically to this one as well, including the reasons, from this perspective, for the FDA's reviews; but because of time, I will just say please include those materials in the comments here.

Second, I will say particularly when it comes to this substance, FDA is trying to have its cake and eat it, too. I say that in that perspective because you heard in the situation, every study that FDA just referenced, an increase in IGF-1. You don't have to take my word for it; go back and look at FDA's own data; yet, they say that it's not effective.

Second, they come to the safety purposes and say that this product should be considered for safety reasons because IGF-1 has increased. In this situation, either the product increases IGF-1

or it doesn't, and if it doesn't, there wouldn't be the safety concern associated with that. So in that perspective, I ask the question again. If every study that has been shown increases IGF-1 -- I'm not saying it showed its ultimate endpoint; I'm saying it increased IGF-1 -- that discusses a potential moving forward. Second, if that's the case, it plays directly into the safety discussion because FDA admits and points to IGF-1 as its safety concerns moving forward.

Third, from this perspective, I would point out that this substance is oftentimes used in the female population. In fact, this is one that is used for bone loss, particularly going through menopause or after menopause, including body mass index. My understanding from this administration, and public statements from many people in this room, is that no regulator should ever stand between a woman and her doctor; yet, I guess we should make a caveat to that statement when it comes to compounded medications because we're taking away a patient's choice when it comes to

this.

Ibutamoren specifically is the substance well characterized. FDA's own GSRS and NIH's own PubChem have a detailed listing for ibutamoren that includes information on the characterization of ibutamoren, both physically and chemically. Again, we have provided the standards in this perspective. If the COAs that we provided are reviewed in written material, you will see endotoxin testing is done underneath ICH standards. You will see, in this case, purity standards, including aggregates, are done, and it is possible to test for chirality. The question that was asked in the PCAC is a great one. FDA in this perspective is not able to point to a specific chiral molecule or to which one is actually effective here; yet, we can still do that testing.

Second, has the substance been used historically in compounding? Unlike the last substance, this one's been dispensed over 500,000 times, over half a million dispensers of prescriptions, and that's just from 9 pharmacies;

that's not the universe here.

Three, are there concerns about whether a substance is effective for a particular use? I will repeat, it has been used over 560,000 times. In addition, there are multiple manufacturers who have reviewed this substance. Merck, as you heard, is 677. There's also another one that we'll get into here in a second.

As was mentioned in the very first presentation by FDA, "When an IND is filed --" I'm going to read off FDA's own slide -- "this includes drug substances and drug product information or letters of authorization that include information for identity, purity, strength and quality, stability, and distribution. It also includes protocols that look at safety and efficacy, including a rationale for the intended use of the drug and evidence that the drug is reasonably safe to use at the dose and duration proposed," end.

Now, in that perspective, if somebody were to follow the same protocols that were used, it would be pretty hard from that perspective to say

FDA would move forward with an IND and allow it to be used in humans, and that's safe and effective, but it wouldn't be for every compounded use moving forward from that.

Is the substance identified consistently based on its physical and chemical characteristics? As I mentioned before, the issues raised by FDA in this situation, for example, chirality, applied to the API and not the compounding in and of itself. If FDA is truly concerned about the product in the API, police guidance documents; discuss the testing. We have the ICH guidance documents. We have FDA's own guidance documents on endotoxin, purity, et cetera, aggregates, going down, which are COAs, which we submitted to the record and show have been met. In addition, there are the links to the PubChem and GSRS for identification purposes of the molecule.

Here are the links to those. Accordingly, chiral purity can be done. We've dropped a footnote here as to how it can be done, and in fact it is an easy study to be done, including a link

here in the record. Two, for the impurities perspective, consistent with the small amounts that are used for ANDAs, which is FDA's standard for ANDAs, that can also be met, and we have pulled that standard from the ANDA guidance documents from the agency itself, which our COAs show can be met.

Third, the residual solvents, our limits are already set for common solvents. Again, you can see the documentation here from ICH guidance documents, which show have been met in our COA. And I would point out, and FDA pointed this out as well, this peptide, just like the last one, can be taken orally; and investigational oral therapies increased height velocity -- this is a direct quote -- "for children with GH deficiency." Accordingly, this can be an oral product as well.

Has the substance been used historically in compounding? Now, historically, this is in addition to Merck, which was, in this case, passed over and glossed over. Lumos is also studying -- Lumos, LUM-201. In this situation, they additionally have provided additional safety

information, as well as the Merck studies from 677, which we've included here.

I would also point out, as we just pointed out, you can use real-world evidence. FDA said this. They put in a couple of parameters as to how it should be a retrospective study, but we have shown, and the evidence is in the record here, that FDA has approved molecules with sample sizes of real-world evidence with 14 patients. Now, some of those increase up to 908, but has done so as little as 14 patients. We have provided the approvals. In addition, NDAs and BLAs, reviewed and approved by FDA from 2019 to 2021, include 13 examples of real-world evidence with reviews of insight into how real world evidence has been used to support regulatory submissions from FDA.

In addition, on this perspective, there's been a discussion on safety, which I'm going to turn over to Jim here in just a second. But it's important to remember that FDA has considered ibutamoren not just in and of itself for those two, but if you actually go to the approval of

macrimorelin, you will see that FDA again includes the review of ibutamoren's safety data. In addition, sermorelin, which can be used in this perspective, has references to ibutamoren as well for their data.

We are also unaware of any serious, let alone unexpected, adverse events directly attributed to drug products compounded from ibutamoren. This includes real-world evidence from pharmacies who have dispensed over 560,000 prescriptions involving this product, half a million-plus. And I will say from this perspective, this was a retrospective analysis where we went back and looked. We have asked the pharmacies if they had safety data, would they have reported it. Yes, they would have reported it from that perspective. This also includes the review from the FAERS and CAERS system as well.

I would also point out, as to the safety perspectives, once a new drug application is filed -- this is from FDA -- an FDA review team evaluates whether the studies the sponsor submitted

show that the drug is safe and effective for its proposed use. Quote, "No drug is absolutely safe. All drugs have side effects. Safe in this sense means that the benefits of the drug appear to outweigh the known risks."

It's important to remember in the situation, we have a prescription. There is a physician who will be overseeing this. This is not something that the patient just takes by themselves. So in this situation, there is somebody who will be monitoring this risk, and they have made the clinical determination and decision that this is needed for her, for the patient.

Here is an example, on the slide in this perspective, of over 500,000 dispenses. Again, this written material has been provided to the FDA in the docket. We have collected aggregated pharmacy dispensing data from 9 pharmacies, and you can see three of them are zero; so in reality, it's six pharmacies alone. We are not aware of any adverse events reported on ibutamoren. They have policies that would require reporting in this

perspective, and all six have told us that they would, in fact, report, either through MedWatch and to the FDA directly, but there weren't issues associated with this product.

With that, I'm going to turn it over to Jim.

MR. LaVALLE: Jim LaValle, clinical pharmacist, Chair of the National Peptide Society, brought here through FarmaKeio. I think I'm just going to try to add color in the time.

What's the time remaining?

DR. GULUR: Three minutes and 19 seconds.

MR. LaVALLE: Perfect.

Obviously, the uses were reviewed previously. I think there are a couple of uses that I want to speak to on the studies. In this 2008, double-blind, randomized, placebo-controlled trial, looking at ghrelin mimetic, the prevention and decrease of fat mass and also decreased abdominal visceral fat in young adults. I think one point is that for individuals that are over the age of 55, increased appetite may be a benefit if they've got sarcopenia. It tends to be reported as

a transient increase in appetite across a couple of these studies.

Obviously, it's been shown that it enhances growth hormone secretion. I have to agree that IGF-1 can be tricky to assess. It similarly increased free-fat mass and decreased abdominal visceral fat in healthy adults over 12 months. The other thing I might mention is that in clinical practice, we teach at the International Peptide Society about 800 members now. This is typically something that is pulsed, meaning they're on it for 6 weeks or so, and then off, so that may alter that 12-month dosing that is typically seen in studies.

Safety here on this study, once again -- let's go to another slide, as that one has already been covered.

Here, daily MK-677 increased both IGF-1 and GH in older adults; increased, once again, free-fat mass; decreased abdominal fat. The insulin sensitivity declined, so a 5-milligram increase in glucose; however, that in another study was reported to be transient both on edema, so the

lower extremity edema was also thought to be transient, as well as the muscle pain was thought to be transient.

This was LUM-201, idiopathic pediatric growth hormone deficiency interim analysis, once again, just the objectives here to see if it was effective. No treatment-related serious adverse events; no meaningful safety signals observed in either of the laboratory values, adverse event data, or in the ECG values.

I believe this was covered. I think the one aspect of this, if we look on this phase 2B trial, if you look at 24 weeks, stair climbing improved, gate speed increased, and MK-677 patients experienced fewer falls than placebo. So even though some of these secondary measures may not show up as important, I think it was important to point out in this particular study, and I think those were pretty significant results.

One or more adverse events reported. This was, I think, one of the more tales of caution, although we saw that 7 patients on the MK-677 group

got a discontinue-it due to adverse events versus 6.6 percent, and if you look, a greater number of patients with myalgia and arthralgia in MK-677 versus placebo. Adverse events that were considered were severe but were not considered by the investigator to be related to the study of the drugs. I think that was mentioned previously as well.

DR. GULUR: If you would like to conclude since you're out of time.

MR. LaVALLE: That's fine. Thank you.

DR. GULUR: Alright. Thank you.

DR. ROSEBUSH: Can we put up just the last slide so they can see your conclusions, please?

DR. GULUR: Yes.

DR. ROSEBUSH: Thank you.

Clarifying Questions from the Committee (con't)

DR. GULUR: The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

Since we do have some additional time, at this point, we will now take remaining clarifying

questions. Again, when acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

Do we have any clarifying questions or comments from the FDA?

Yes?

DR. GANLEY: Hi. I'm Charlie Ganley. I mentioned this in the previous session, but there are members here that were not present earlier, so I'm going to just state it again regarding the issue of real-world evidence.

Real-world evidence is the clinical evidence about the usage and potential benefits or risks of a medical product derived from the analysis of real-world data. Various sources of real-world data can be analyzed in non-interventional studies, including registries, electronic health records, and medical claims.

The information provided in the presentation are simply numbers of prescriptions filled by unidentified pharmacies, and it wasn't clear over

what total period of time that involved. Most importantly, it does not provide any data related to the safety and effectiveness of the drug, so simply providing the number of prescriptions is not sufficient. And I will note, in the open public hearing, on slide 13, even though there were 562,000 prescriptions, we are not aware of any adverse event reported on ibutamoren; and it was evident in the clinical trials that were discussed during the FDA presentation that there are adverse events. So simply collecting prescription information is not representative of safety of the product; you have to have reporting of it.

I think there was a comment regarding the pharmacies will report them. There's no requirement for them to report them to FDA. I think the other thing is there's a disconnect here between this exposure data and no adverse event reported; yet, it's clear just from the pharmacologic action of the drug that you're going to see adverse events in some patients. Thank you.

DR. GULUR: Thank you.

Any other clarifying questions? Virtual?

(No response.)

Committee Discussion and Vote

DR. GULUR: So at this point, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will now proceed with questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel. After I read each question, we will pause for any questions or comments concerning its wording.

FDA is proposing that ibutamoren mesylate not be included on the 503A Bulks List. Should ibutamoren mesylate be placed on the list?

We will be using an electronic voting system for this meeting. Once we begin the vote, the buttons will start flashing and will continue to flash even after you have entered your vote.

Please press the button firmly that corresponds to your vote. If you are unsure of your vote, or you wish to change your vote, you may press the corresponding button until the vote is closed. After everyone has completed their vote, the vote will be locked in.

The vote will then be displayed on the screen. The DFO will read the vote from the screen into the record. Next, we will go around the room, and each individual who voted will state their name and vote into the record. You can also state the reason why you voted as you did, if you want to. We will continue in the same manner until all questions have been answered or discussed.

Question 2. FDA is proposing that ibutamoren mesylate not be included on the 503A Bulks List. Should ibutamoren mesylate be placed on the list? If you vote no, you are recommending FDA not place the bulk drug substance on the 503A Bulks List. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding

under Section 503A unless it becomes the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug.

Any discussion? Any clarifying questions on the vote before we proceed?

(No response.)

DR. GULUR: Everyone's comfortable?

(No audible response.)

DR. GULUR: Wonderful.

If there are no further questions or comments concerning the wording of the question, we will now begin the voting process. Please press the button on your microphone that corresponds to your vote. You will have approximately 20 seconds to vote. Please press the button firmly. After you have made your selection, the light may continue to flash. If you are unsure of your vote or you wish to change your vote, please press the corresponding button again before the vote is closed.

(Voting.)

DR. GULUR: We will be waiting for all the

votes to be counted, including virtual members, who will be sending their votes in by email. I thank everyone for their patience.

(Pause.)

DR. STEVENSON: Good morning. Takyiah Stevenson, DFO. For the record, we have 1 yes, 13 noes, and zero abstentions. Thank you. I'll hand it back to the chairperson.

DR. GULUR: Now that the vote is complete, we will go around the table and have everyone who voted state their name, vote, and if you want to, you can state the reason why you voted as you did into the record. We will start with the person at the end of this table.

Dr. Newman? Sorry. Dr. Weber?

DR. WEBER: Thank you. This is Tom Weber. I voted no. I did not think that the efficacy was sufficient to warrant approval on the list versus the safety of the compound.

DR. NEWMAN: This is Connie Newman. I voted no. There was not sufficient evidence for effectiveness in all of the disorders that were

studied. In particular, I'm concerned about the safety of giving this product to people because of the adverse effects that have been seen and that are very likely due to excess growth hormone. We see these adverse effects in our patients with pituitary tumors secreting growth hormone. I'm particularly concerned about the fluid retention; the congestive heart failure; myocardial infarction; hyperglycemia; and the risk of diabetes, and those are among the reasons that I voted no.

DR. COOKE: This is David Cooke. I voted no, in large part because of a lack of sufficient safety data, particularly long-term safety data for a compound that likely would be used for extended periods of time for many of the indications suggested, as well as a lack of evidence of efficacy. The rise in IGF-1 as a surrogate endpoint is perhaps an interesting one, but certainly didn't see data of actual clinical efficacy.

DR. BILLINGTON: Charles Billington. I

voted no. Similar to my colleagues, I will accept the notion that IGF-1 may rise in at least a fraction of the patients treated, but whether that correlates with the outcomes for which it was specifically proposed is very unclear. The evidence is not very good for any of the stated purposes. I also agree and have concerns about long-term safety because that really has not been sufficiently characterized. So we just don't know enough about this to take this step.

DR. WEISS: I'm Rita Weiss. I voted no for the reasons already stated by these esteemed colleagues. There's just not safety and efficacy to support this.

DR. SERUMAGA: Brian Serumaga from the USP. I voted no for the reasons that have been stated earlier. Also, in addition, there is no USP monograph for this. As was mentioned earlier, there was a request to make a USP monograph for this particular item, and just to remind everybody, USP is not a regulator. There is a process through which new drugs are approved in the monograph

development process at USP. Particularly for component preparation, monographs cannot be used to circumvent the new drug approval process that is required in federal law. So I voted no for those reasons.

DR. BOGNER: Robin Bogner. I voted no for some of the safety concerns already mentioned.

DR. GURA: Kathleen Gura. I voted no for the same reasons the others before me stated. I have safety concerns.

DR. VAIDA: Allen Vaida. I voted no for one of the reasons that were discussed, especially the adverse effects on that; and I'm not quite sure they are really all the effects that have happened.

DR. DURHAM: I'm Todd Durham. I voted no for the same reasons mentioned previously.

DR. GULUR: Dr. Desai was here virtually. Would you mind stating your name and vote?

DR. DESAI: Yes. Hi. Seemal Desai, dermatologist, University of Texas Southwestern and the founder of Innovative Dermatology. Just for the record for the meeting today, I am the

President of the American Academy of Dermatology, but none of my views represent the views of the academy.

I voted yes. I actually felt that there was quite interesting data that certainly showed extensive use previously, and in particular, I found the pediatric data to be quite sufficient. So for those reasons, I actually voted yes.

DR. GULUR: Thank you.

Dr. Rebello?

DR. REBELLO: Elizabeth Rebello, MD Anderson Cancer Center. I voted no for the aforestated reasons discussed prior regarding safety and efficacy.

DR. GULUR: Thank you.

Dr. Yanovski?

DR. YANOVSKI: I voted no for the previously stated reasons. Thank you.

DR. GULUR: Thank you.

I'm Padma Gulur, and I voted no for the reasons stated by other members of this committee already, and I would also like to state for the

record that the lack of the USP monograph alone is not the reason for my vote for no.

Adjournment

DR. GULUR: With that, I'd like to summarize again that we have 13 committee members voting no to adding this to the bulks drug list, and one member voting yes.

With this, we end this topic, and we will be now breaking early for lunch. We will reconvene at 12; otherwise, we were going to have an hour and a half for lunch, and I think we're all ok without that, if everyone agrees. Thank you.

(Whereupon, at 10:55 a.m., the topic 2 session was adjourned.)