FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Monday, November 20, 2017

8:30 a.m. to 12:54 p.m.

Morning Session

FDA White Oak Campus

White Oak Conference Center

10903 New Hampshire Avenue

Silver Spring, Maryland

Meeting Roster

DESIGNATED FEDERAL OFFICER (Non-Voting)

Cindy Chee, 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

Michael A. Carome, MD, FACP

(Consumer Representative)

Director of Health Research Group

Public Citizen

Washington, District of Columbia

Gigi S. Davidson, BSPh, DICVP

(U.S. Pharmacopeial Convention Representative)

Director, Clinical Pharmacy Services

North Carolina State University

College of Veterinary Medicine

Raleigh, North Carolina

Seemal R. Desai, MD, FAAD

(Participation in 7-keto DHEA, astragalus, epigallocatechin gallate, and resveratrol discussion)

President and Medical Director

Innovative Dermatology

Plano, Texas

Padma Gulur, MD

(Acting Chairperson)

Vice Chair, Operations and Performance

Duke University School of Medicine

Department of Anesthesiology

Duke University Medical Center

Durham, North Carolina

Stephen W. Hoag, PhD
Professor
Department of Pharmaceutical Science
University of Maryland, Baltimore
Baltimore, Maryland

William A. Humphrey, BSPharm, MBA, MS
Director
Pharmacy Operations
St. Jude Children's Research Hospital
Memphis, Tennessee

Elizabeth Jungman, JD
Director
Public Health Programs
The Pew Charitable Trusts
Washington, District of Columbia

Kuldip R. Patel, PharmD
Associate Chief Pharmacy Officer
Duke University Hospital
Durham, North Carolina

Jurgen Venitz, MD, PhD
(Participation in L-citrulline, pregnenolone, 7-keto DHEA, astragalus, and epigallocatechin gallate discussion via phone)
Professor and Vice Chairman
Virginia Commonwealth University
School of Pharmacy, Department of Pharmaceutics
Richmond, Virginia

Allen J. Vaida, BSc, PharmD, FASHP
(Participation in L-citrulline, pregnenolone, astragalus, epigallocatechin gallate, and resveratrol discussion)
Executive Vice President
Institute for Safe Medication Practices
Horsham, Pennsylvania

Donna Wall, PharmD

(National Association of Boards of Pharmacy

Representative-Participation via phone)

Clinical Pharmacist

Indiana University Hospital

Indianapolis, Indiana

PHARMACY COMPOUNDING ADVISORY COMMITTEE MEMBERS

(Non-Voting)

Ned S. Braunstein, MD

(Industry Representative)

Senior Vice President and Head **of Regulatory Affairs**

Regeneron Pharmaceuticals, Inc.

Tarrytown, New York

William Mixon, RPh, MS, FIACP

(Industry Representative)

Former Owner, The Compounding Pharmacy

Hickory, North Carolina

TEMPORARY MEMBERS (Voting)

Kenneth D. Burman, MD

(Participation in L-citrulline, astragalus, epigallocatechin gallate, and resveratrol discussion)

Chief, Endocrine Section
Medstar Washington Hospital Center
Professor, Department of Medicine
Georgetown University
Washington, District of Columbia

Jess G. Fiedorowicz, MD, PhD

(Participation in pregnenolone discussion via phone)

Associate Professor
Departments of Psychiatry, Epidemiology and Internal Medicine
University of Iowa Carver College of Medicine
Iowa City, Iowa

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(8:30 a.m.)

Call to Order

Introduction of Committee

DR. GULUR: Good morning, everyone. I would first like to remind everyone present to please silence your cell phones, Blackberries, and other devices if you have not already done so. I would also like to identify the FDA press contact for this open-session meeting, Ms. Lyndsay Meyer. If you are present, please stand.

Good morning. My name is Padma Gulur. I am the acting chairperson of the Pharmacy Compounding Advisory Committee, otherwise referred to as PCAC. I will now call the committee to order.

We will now ask those at the table, including FDA staff and the committee members, to introduce themselves starting with the FDA representative to my far left and moving along to right side, ending with one of the industry representatives, Dr. Ned Braunstein.

DR. DOHM: Hi. My name is Julie Dohm, and

I'm the agency lead on compounding.

MS. BORMEL: I'm Gail Bormel from the Office of Unapproved Drugs and Labeling Compliance in CDER's Office of Compliance.

DR. LAWSON: I'm Rosilend Lawson, also from the Office of Unapproved Drugs and Labeling Compliance in CDER compliance.

MS. ROTHMAN: Sara Rothman, CDER's Office of Unapproved Drugs and Labeling Compliance.

DR. GANLEY: Charlie Ganley from the Office of New Drugs in CDER.

DR. JOHNSON: Sue Johnson, Office of Drug Evaluation IV, Office of New Drugs, CDER.

DR. FURLONG: Good morning. I'm Leslie Furlong, deputy director, Office of Drug Evaluation IV in CDER.

DR. HARROUK: My name is Wafa Harrouk. I'm a pharmacologist in ODE IV, CDER.

DR. BURMAN: Ken Burman, chief of endocrinology at MedStar Washington Hospital Center and professor at Georgetown University.

DR. VAIDA: Allen Vaida, a pharmacist at the

Institute for Safe Medication Practices.

DR. GULUR: Dr. Venitz, are you on the phone?

DR. VENITZ: Yes. Jurgen Venitz, clinical pharmacologist, Virginia Commonwealth University.

DR. CHEE: Cindy Chee, DFO for PCAC.

MS. DAVIDSON: Gigi Davidson. I represent the United States Pharmacopeia.

MR. HUMPHREY: William Humphrey. I'm the director of pharmacy operations at St. Jude Children's Research Hospital.

DR. PATEL: Kuldip Patel, associate chief pharmacy officer at Duke University Hospital.

DR. BOGNER: Robin Bogner, professor of pharmaceutics, University of Connecticut.

DR. GULUR: We're just going to step back here.

Dr. Wall, are you on the phone?

DR. WALL: Yes. I'm on the phone.

DR. GULUR: Could you introduce yourself?

DR. WALL: Donna Wall. I represent NABP. I'm a pharmacist at Indiana University Hospital in

Indianapolis, Indiana.

MS. JUNGMAN: Elizabeth Jungman. I direct public health programs at the Pew Charitable Trust.

DR. HOAG: Hello. I'm Steve Hoag. I'm a professor at the University of Maryland School of Pharmacy.

DR. CAROME: I'm Mike Carome, director of Public Citizens Health Research Group.

MR. MIXON: Bill Mixon, compounding pharmacist from Hickory, North Carolina, non-voting industry member.

DR. BRAUNSTEIN: Ned Braunstein. I'm senior vice-president for regulatory affairs and safety at Regeneron Pharmaceuticals, and I'm the non-voting industry representative.

DR. GULUR: Thank you, everyone.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's 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 reminder, individuals will be allowed to speak into the record only if recognized by the chair. 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 the 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.

Today, we will cover six bulk drug substances nominated for inclusion on the list of bulk drug substances that may be used to compound drugs in accordance with Section 503A of the Food, Drug, and Cosmetic Act: L-citrulline, pregnenolone,

7-keto-dehydroepiandrosterone, astragalus, epigallocatechin gallate, and resveratrol.

For each of the six substances, we will hear presentations from the FDA, ask clarifying questions, hear nominators' presentations, ask clarifying questions, hold an open public hearing, and have committee discussion and voting.

As described in the October 26, 2017 Federal Register notice, the committee will be discussing six bulk drug substances nominated for inclusion on the Section 503A bulks list. The Federal Register notice identified the uses FDA reviewed for each of the six bulk drug substances being discussed at this meeting.

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

The nominators of these substances have been invited to make a short presentation supporting their nomination. To the extent that the

nominators' presentations include information about additional uses, dosage forms, and routes of administration, I remind the committee that these additional uses, dosage forms, and routes of administration are not part of the agency's review because the nominators either did not nominate those uses, dosage forms, and routes of administration, or they were not adequately supported.

Let us begin. We will now have Dr. Cindy Chee read the conflict of interest statement.

Conflict of Interest Statement

DR. CHEE: The Food and Drug Administration is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the National Association of the Board of Pharmacy, the United States Pharmacopeia, and of the industry representatives, all members and temporary voting members of the committee are special government employees 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 the 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 the 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 his or her potential financial conflict of interest or when the interests 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 interest 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 meeting, the committee will discuss six bulk drug substances nominated for inclusion on the Section 503A bulks list. FDA will discuss the following nominated bulk drug substances and the uses FDA reviewed: astragalus for allergic rhinitis; asthma, diabetes, herpes simplex keratitis, wound healing; L-citrulline for hyperammonemia due to cycle disorders; pregnenolone for rheumatoid arthritis, hypercholesterolemia, manic and depressive symptoms of bipolar disorder, and bipolar disorder with substance abuse, dual

diagnosis, positive and negative symptoms of schizophrenia; 7-keto-dehydroepiandosterone for weight loss and in Raynaud's phenomena; epigallocatechin gallate for treatment of obesity, wound healing, corneal neovascularization, non-alcoholic fatty liver disease, cardiac hypertrophy, diabetes type 1 and 2, and Parkinson's disease; and resveratrol for treatment of older adults with impaired glucose tolerance and pain.

The nominators of these substances will be invited to make a short presentation supporting the nomination.

This is a particular matters meeting, during which specific matters related to the six bulk drug substances will be discussed. Based on the agenda for today's meeting and all financial interests reported by the committee members and temporary voting members, no conflict of interest waivers have been issued in connection with this meeting.

We would like to note that Dr. Allen Vaida has been recused from participating in the discussions and voting for the 7-keto-DHEA session

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

We would like to note that Dr. Donna Wall is a representative member from the National Association of the Board of Pharmacy and Ms. Gigi Davidson is a representative member from the United States Pharmacopeia.

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 NAPB and the USP. Their role is to provide the committee with the points of view of the NAPB and the USP.

Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment in the particular matters at issue. Instead, they serve as the voice of the NAPB and USP, entities

with financial or other stakes in the particular matters before the advisory committee.

With respect to FDA's invited industry representatives, we would like to disclose that Dr. Ned Braunstein and Mr. William Mixon are participating in this meeting as non-voting industry representative, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Braunstein is employed by Regeneron Pharmaceuticals, and Mr. Mixon is employed by the Compounding Pharmacy.

We would like to remind members and temporary voting members that if the discussions involve any other bulk drug substances 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 other participants to advise the committee of any financial relationships

that they may have with the topic at issue that could be affected by the committee's discussions. Thank you.

DR. GULUR: We will now proceed with FDA introductory remarks from Dr. Julie Dohm, who is the agency lead on compounding for the FDA.

FDA Introductory Remarks – Julie Dohm

DR. DOHM: Thank you. I'd like to welcome everyone to the eighth meeting of the Pharmacy Compounding Advisory Committee. Today, we will discuss six bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding under Section 503A. They are L-citrulline, pregnenolone, 7-keto-DHEA, astragalus extract 10:1, EGCg, and resveratrol.

Tomorrow, we will present two categories of drug products nominated for placement on the list of drug products that cannot be compounded under Sections 503A or 503B because they present demonstrable difficulties for compounding, liposomal drug products and drugs produced using hot melt extrusion.

As in the May meeting, we have scheduled time for the nominators to speak and time for an open public hearing after each topic. I would also like to use this opportunity to provide you with an update on a document issued by the agency since the committee last met in May in response to stakeholder feedback that is pertinent to one of the topics discussed during a PCAC meeting.

In July, FDA published a notice to establish a new public docket so that interested parties can nominate drug products or categories of drug products for inclusion on the difficult-to-compound list that were not previously nominated, resubmit previous nominations with additional supporting information, or submit comments.

Nominations and comments may be made to this docket at any time. We will present new nominations to the advisory committee for discussion as we evaluate them. The Federal Register notice opening this docket appears on the FDA's compounding website under the section titled Regulatory Policy Information.

Again, thank you for your participation on the Pharmacy Compounding Advisory Committee. We look forward to a productive meeting and to continuing to work together. Thank you.

DR. GULUR: Thank you, Dr. Dohm.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the committee.

We will now proceed with an FDA presentation on L-citrulline from Dr. Johnson.

FDA Presentation – Susan Johnson

DR. JOHNSON: Good morning. Thanks for joining us. While the turkey is defrosting at home, we appreciate you fitting us into your busy holiday schedules.

My name is Susan Johnson, and I'm from the Office of Drug Evaluation IV in CDER's Office of New Drugs. The first nominated substance that we'll be discussing is L-citrulline.

I'd like to thank members of the review

team, especially review staff in the Division of Gastroenterology and Inborn Error Products, and Dr. Jarow from the Center Director's office.

L-citrulline has been nominated for inclusion on the 503A list and has been proposed for oral use in the treatment of urea cycle disorders or UCDs. L-citrulline is a non-essential amino acid that's used in the body in the L enantiomer form. It is a well-characterized substance that is soluble in water. It is likely to be stable as a solid or liquid under ordinary storage conditions.

L-citrulline is primarily produced by fermentation, but can also be synthesized. The synthesis reaction is complex and involves potentially toxic reagents. As noted in the review, compounders should use the information about impurities identified in the certificate of analysis accompanying the bulk drug substance to evaluate any potential safety, efficacy, or quality issues.

In conclusion, L-citrulline is well

characterized and likely to be stable under ordinary storage conditions as a solid or liquid for oral dosing.

We usually discuss the history of use of a nominated substance toward the end of our presentations, but before we delve into the safety and efficacy of L-citrulline, we wanted to clarify that it has been used to treat certain UCDs for at least 30 years.

L-citrulline is currently available as a dietary ingredient in dietary supplement products. We don't have sufficient information to discern the extent to which L-citrulline is compounded, but the UCD population includes neonates, and it's likely therefore that the marketed dietary supplement products will not meet their dosing needs.

There are published practice guidelines that support L-citrulline's use in the treatment of these rare diseases. L-citrulline is found in many foods and is not considered an essential amino acid because it can be synthesized endogenously in healthy humans.

It's an intermediate in the urea cycle, which is the predominant process in humans for nitrogen disposal. L-citrulline has other functions in the body. For instance, it's a precursor for L-arginine, which is in turn a precursor for nitric oxide, which has various cardiovascular activities.

This is a diagram of the urea cycle that functions in two subcellular compartments, the mitochondrial matrix and the cytosol to convert ammonia into urea that is excreted by the kidney. We'll look at the urea cycle again as we discuss the efficacy of L-citrulline.

Non-clinical pharmacokinetic data has shown that intravenous doses of L-citrulline pass through the placenta to the fetus in sheep. The pharmacokinetics of L-citrulline following oral dosing in healthy adults so that it's absorbed, produces a dose-dependent AUC, and has a short elimination half-life. Levels of arginine are also observed to increase following L-citrulline dosing.

Acute and repeat dose non-clinical safety

studies showed little toxicity at doses up to 830 milligrams per kilogram. We were not able to find non-clinical genotoxicity or carcinogenicity studies or developmental and reproductive toxicity studies for L-citrulline.

Looking at clinical safety and voluntary adverse events, the FAERS system provided 15 unique reports. Of these, 9 reported events were associated with a subpotent batch of L-citrulline as a bulk chemical. The potency issue was detected after 2 UCD patients unexpectedly experienced hyperammonemia within a short period of time while receiving L-citrulline therapy with a product from the same supplier. The L-citrulline product that the patients had received was assayed, found to contain no L-citrulline, and was recalled. Details of this event were described in a published article.

There were 332 reports from the CAERS system. Although 3 deaths and multiple serious reactions were reported, causality assessment is not possible due to the use in each case of

multiple products or products containing multiple ingredients.

We found no clinical trials of safety or efficacy in UCDs. However, we found many publications describing the use of gram quantities of L-citrulline to treat UCDs, and none of these publications described associated toxicities.

We found one clinical trial of the use of oral L-citrulline in the treatment of erectile dysfunction. Twenty-four patients were treated with 1.5 grams of oral L-citrulline daily for a month, and no adverse reactions were reported.

In conclusion, we have limited safety information from non-clinical and clinical trials, so long-term issues in particular cannot be ruled out. However, decades of clinical use in the treatment of UCDs has not been associated with known safety concerns.

Turning to the efficacy of L-citrulline for the treatment of urea cycle disorders, UCDs are a group of rare diseases, predominantly enzyme deficiencies, that are due to inborn errors. An

estimate of accumulated incidence of all 8 UCDs is 1 in 35,000 births in the U.S. Some of the diseases have an incidence of lower than 1 in 2 million live births.

The onset of UCDs is often in the neonatal period. In these cases, there is complete or near complete enzyme deficiency. Estimates of incidents are known to be unreliable, as infants with UCDs often develop severe symptoms rapidly, and the disorders can be fatal before the infant can be diagnosed. When diagnosed in older children and adults, UCDs are associated with partial enzyme deficiencies in which alternative metabolic pathways have provided compensation.

Hyperammonemia is the principal sign of UCDs. The differential diagnosis is intended to elucidate the pattern of related signs and symptoms that match a particular enzyme deficiency. FDA's efficacy assessment considered those UCDs that are amenable to L-citrulline therapy based on a mechanistic rationale and current treatment protocols.

Here's the urea cycle that we saw earlier, and we're focusing on the impact on L-citrulline of the various components of this cycle. Deficiencies in the enzymes active in the mitochondrial matrix such as N-acetyl glutamate synthetase result in decreased production of citrulline precursors, and in turn, citrulline. Similarly, deficiency of carbamoyl phosphate synthetase 1 produces a reduction in citrulline, as does a deficiency in ornithine transcarbamylase.

The urea cycle cannot function unless there is ornithine in the mitochondria. In HHH syndrome, there is a defect in the mitochondrial ornithine transporter, resulting in hyperornithinemia, hyperammonemia, and homocitrullinuria, which is urinary excretion of homocitrulline.

Certain other UCDs are associated with increased plasma levels of citrulline and are not therefore amenable to L-citrulline supplementation. One example is argininosuccinate synthetase deficiency, also called citrullinemia type 1. Citrullinemia type 2 is caused by a deficiency of

the amino acid transporter citron. As with citrullinemia type 1, it is not appropriate to introduce exogenous citrulline as part of therapy.

To help clarify the role of L-citrulline, we wanted to provide an overview of the treatment of UCDs. The primary goal is to reduce hyperammonemia and prevent its reoccurrence. Nitrogen scavengers facilitate clearance of circulating ammonia, and it includes sodium benzoate, sodium phenylacetate, and sodium phenylbutyrate. These are available in FDA-approved products.

Treatment also includes limiting dietary intake of certain amino acids in conjunction with supplementation of other amino acids. As we've discussed, the choice to use L-citrulline in contrast to L-arginine is dependent on the specific UCD deficiency. L-arginine is approved in an FDA injectable product. L-citrulline is currently available as a dietary ingredient in dietary supplement products and is compounded. Carglumic acid is an NAG analogue that is FDA approved for use in NAG synthetase deficiency.

To summarize, oral L-citrulline is a standard of care in certain urea cycle disorders. Based on the strong mechanistic rationale and decades of successful treatment, there are published dosing recommendations to guide therapeutic use. While we found no clinical trials that evaluated the use of L-citrulline in treatment of UCDs, we conclude that oral L-citrulline is effective in the treatment of certain urea cycle disorders.

We also want to identify that there is information in the public domain that an IV L-citrulline product is currently being studied under an IND for use during pediatric congenital heart surgery to decrease cardiovascular and pulmonary morbidity.

L-citrulline is well characterized and stable. It has at least a 30-year history of being compounded for use in the treatment of UCDs. We acknowledge the lack of non-clinical information regarding potential long-term effects of treatment of L-citrulline. However, in its length of history

of clinical use in serious rare diseases, it has not been associated with significant adverse events.

In the absence of clinical trials, successful treatment with certain urea cycle disorders is reliably achieved with L-citrulline. A balancing of the four evaluation criteria weighs in favor of L-citrulline for oral administration being added to the list of bulk drug substances that can be used for compounding under Section 503A.

I'm happy to take any of your questions.

Clarifying Questions from the Committee

DR. GULUR: At this time, we will accept clarifying questions from the committee. We ask that you limit your questions to clarifications only. Members will have further opportunity for discussion and questions after we have heard all of the presentations. Any questions?

(No response.)

DR. GULUR: Any questions from our members on the phone?

(No response.)

DR. JOHNSON: Thank you, Dr. Johnson.

DR. GULUR: We will now proceed with the nominator presentations. We have one present, Dr. A.J. Day from PCCA.

Nominator Presentation – A.J. Day

DR. DAY: Good morning. My name is A.J. Day with PCCA. As a conflict of interest statement, PCCA is a wholesaler that does provide L-citrulline powder to the compounding industry.

I'd like to thank FDA for the thorough review of the data behind L-citrulline. One of the things that were mentioned in the briefing document from the FDA was the source of L-citrulline. The material that PCCA utilizes comes from an FDA-registered and inspected CGMP facility, and the mechanism of production is by the fermentation pathway, which was discussed previously.

The common dosage range that's used clinically is around 500 to 650 milligrams, but of course this is weight-based dosing. The reason that this needs to be compounded is because, as

Dr. Johnson mentioned, many of these patients are neonates and pediatric patients, so getting the appropriate dose into a dosage form that they can swallow is very important.

Sometimes these are going via tubes. Very often these patients have metabolic disorders, so their ability to process multiple ingredients is oftentimes impaired, and they need a lot of different supplementations. So we're limited under the amount of volume of medications that they can have to begin with. So that's really the population for whom compounding L-citrulline is necessary.

Because of the uniqueness of the urea cycle disorders, the physicians who specialize in this are relatively limited and so are the pharmacists. So there may be pharmacies in certain pockets of the country who do this and others who are completely not familiar with it. Because of that ability to specialize and being very cognizant of the concerns and the appropriate types of urea cycle disorders, only a handful of pharmacies

across the country may be appropriate to make these.

So that becomes relevant for another component of the FDA's implementation of the Drug Quality and Security Act, which is the memorandum of understanding and how we can get this medication from those specialty pharmacies to patients across the country.

With that, I will conclude my incredibly brief presentation.

Clarifying Questions from the Committee

DR. GULUR: We will now entertain clarifying questions from the nominator from the committee. Dr. Burman?

DR. BURMAN: Just a clarification of the dose. You said 500 to 650 milligrams, and then said something about it's changed based on the weight of the infant or the child. Could you speak a little more about that?

DR. DAY: In preparation for this discussion, I contacted some of the pharmacies who are compounding this to find out what kind of

common doses they're utilizing. And they gave me that as a range of some of the typical prescriptions that they'd seen, but they had the very strong caveat that that's based off of the weight of the patients for whom it's being prescribed.

So they do see things that are outside of that range, but if I needed to express a common dosage, that range is where they see a lot of the prescriptions falling.

DR. GULUR: Dr. Vaida?

DR. VAIDA: This was originally put up for IV use, the original some of the submissions, and then it was changed to oral. In your review of compounding pharmacies, have you found any that still use an IV? The FDA reported that they had some uses when they actually went on the internet.

DR. DAY: I am not aware, and I have not been able to find any indications of IV utilization. I've not found any formulas or promotions of IV use in my search. The original nomination that mentioned IV use was -- again, we

have this conversation, I feel like, at most of these PCAC meetings.

When the nominations were first asked for, it was for all the potential uses. And upon finding the IND that is on file with the FDA -- and there is clinical research out there about IV utilization -- that was included as a potential use.

In our review of the materials for really practical uses, what is it currently being compounded for, there's no indication that it's being utilized for any kind of sterile formulations at all.

DR. GULUR: Any questions from our members on the phone?

(No response.)

DR. GULUR: I have one further question as well. Would you like to comment on the subpotent cases that were there, that were reported with L-citrulline and how in your process those reinsure that does not happen?

DR. DAY: So my opinion of that is that it

comes down to the quality mechanisms from the manufacturer and the wholesaler. And something in that process seems to have broken down in that issue, where it was tested and found not to contain L-citrulline in the containers that were marked L-citrulline.

So that was an issue of the quality chain previous to the pharmacy receiving their materials, and that's an issue I feel is under regulation with FDA in the supply chain. And that's something that, at PCCA, we actually have a process internally for our QA/QC, where every single batch of every single chemical, including L-citrulline, gets quarantined until it goes through a full analysis, including IR spec, to identify any potential impurities, to make sure that whatever we're receiving matches the standard.

DR. GULUR: Thank you, Dr. Day.

DR. DAY: Thank you.

Committee Discussion and Vote

DR. GULUR: We are now convening the open public hearing for this. We do not have any open

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

We will now begin the panel discussion of L-citrulline. Any comments?

DR. CAROME: Mike Carome. Just to follow up on the question you just asked and redirected to the FDA, in those cases, were those dietary supplemental formulations associated with those subpotent formulations, or were they compounded products?

DR. JOHNSON: The literature article that was published in association with this eventually found -- of course, their interests were in treating children who needed the L-citrulline and finding that it was not serving the purpose because the children developed hyperammonemia unexpectedly after being stabilized on L-citrulline treatment.

But eventually, the follow-up led to the fact that the bulk substance that was in the bottle was not L-citrulline. The error apparently had come at the bulk substance manufacturer's end of

things, and they had actually put a different amino acid in the bottle labeled L-citrulline.

DR. VENITZ: I have a follow-up question.

DR. GULUR: Yes, Dr. Venitz?

DR. VENITZ: Dr. Day mentioned that they [indiscernible] of the manufacturing of L-citrulline? Can FDA comment on that, on how many manufacturing sites do you have in the U.S.?

DR. GULUR: How many manufacturing sites do we have in the U.S.? Dr. Venitz, is that your question?

(No response.)

DR. JOHNSON: I think Dr. Day might be better able to answer that.

DR. DAY: I cannot speak to the number of manufacturing sites for this product. I can only speak about the supplier that we utilize, the manufacturer that we utilize. They're a Japanese company who has an office, a manufacturing facility in the U.S., and I can't say specifically where this product is initiated and fully produced.

DR. GULUR: Thank you, Dr. Day. Dr. Mixon?

MR. MIXON: Do you know, Dr. Johnson, if the certificate of analysis for that subpotent preparation listed the product or stated the product was L-citrulline when in reality it wasn't?

DR. JOHNSON: I don't know if the published article contained that information. I have it with me, and I can check.

MR. MIXON: Thank you.

DR. GULUR: Dr. Burman?

DR. BURMAN: Maybe for Dr. Day, could you just make sure that I understand or we understand the potential impurities when you prepare L-citrulline by fermentation?

DR. DAY: The extent of my familiarity with the impurities was outlined in the presentation from Dr. Johnson. I don't know if she has more details to provide than that. She may be looking up the previous question about the certificate of analysis.

DR. GULUR: Thank you, Dr. Day. Dr. Ganley?

DR. GANLEY: Yes. The one thing that we need to clarify is that the certificate of analysis

is very important to the compounding pharmacist because the bulk substance is supposed to be produced by or manufactured by an FDA-registered facility, so the compounding pharmacist depends a lot on the accuracy of that information.

Where it may become difficult for a compounding pharmacy is if, for example, there are heavy metals in the production, yet they may not be required to list them specifically, but just a cumulative amount.

So the compounding pharmacist, if they see, for example, heavy metals for much larger amounts than usually allowed under USP, they should be asking questions of the manufacturer. So that's where there is an important relationship between the compounding pharmacy and the bulk manufacturer.

DR. GULUR: Thank you, Dr. Ganley.

Just as a further clarification, Dr. Johnson, is it our understanding that this subpotent report was off of a published article? Was there an actual FDA review of that incident?

DR. JOHNSON: There was, and there's

information on our website about their recall as well. So the certificate of analysis of the L-citrulline product that the patient received through the hospital pharmacy stated 99.88 percent pure L-citrulline and was supplied by a national compounding supplier. That's what the article says.

DR. GULUR: Yes, Dr. Davidson?

MS. DAVIDSON: In the absence of a USP substance monograph, which is why we're having the discussion about this particular substance, where would a pharmacist determine acceptable standards, looking at the certificate of analysis? Would they consult the USP chapters on impurities in general?

DR. GANLEY: I think that's a good question and that's one of the things that we're trying to look into a little further as to what is best practices for compounding pharmacies.

So obviously, when someone manufactures something, there may be differences in the processes. So the certificate of analysis from different manufacturers would look different,

particularly for the impurities. And one option would be to follow USP chapters, for example, on heavy metals, and then ask the manufacturers specific questions regarding that, what may be those heavy metals that are not specific in the certificate of analysis.

But that's where the relationship is important between the compounding pharmacy, and they know that they're going to a reputable manufacturer, and that there has to be a relationship there. I think that's the burden on the compounding pharmacy, to be sure that they know what questions to ask and also be confident in their manufacturer.

We've talked internally, and we can talk to Dr. Day a little bit. We were hoping to put out some guidance to compounding pharmacists for best practices and what are some of the things you need to think about when you're going to a manufacturer.

MS. DAVIDSON: Maybe I can ask Dr. Day this question. So when PCCA produces a certificate of analysis for the citrulline that you're selling, in

my experience, when you look at a certificate of analysis, it says that the substance complies with something. What is the something with which your C of A complies with?

DR. DAY: The original certificate of analysis is produced by the manufacturer. The parameters that they're testing, I don't have specific information on how they develop the parameters for each individual substance.

My belief is that it follows a pathway of logic, so such as looking at the potential impurities, what are the levels that are generally accepted in similar products? And a lot of this -- for example, L-citrulline would be influenced from the dietary supplement industry, so what's allowable under oral utilization may be a significant factor in that decision as well.

At PCCA, we are doing a number of tests to quantitatively and qualitatively compare and verify the information that is on a C of A. We don't take the C of A at face value for reasons such as Dr. Johnson showed, where the material that you

receive in that C of A, what if there's a mistake there? So we need to make sure that we're able to catch that as well as the wholesaler.

DR. GULUR: Any further questions? Yes, Dr. Bormel?

MS. BORMEL: I just had a question for Dr. Day. Does that qualitative analysis also include identity testing of the bulk?

DR. DAY: It does.

MS. BORMEL: Thank you.

DR. GULUR: Dr. Hoag?

DR. HOAG: I was just going to make a comment. People talk about the relationship between the manufacturer and the compounding pharmacist, but I bet that one in a thousand compounding pharmacists actually calls the manufacturer because most of them are in China, and you've got to go through a broker, and also they're not going to deal with small quantities and materials. So probably the most important relationship is between the distributor and the compounding pharmacist.

DR. GULUR: Yes, Dr. Bogner?

DR. BOGNER: On the C of A, I note there's no melting point specification. Melting point is a very nice and easy test that can even be done in the pharmacy and is done in pharmacies in other countries. I'm wondering why there's not a melting point specification. And then I have some other questions regarding the C of A.

DR. DAY: Again, the specific parameters to test are generated by the manufacturer. So if they did not require for this particular substance melting point -- in previous meetings, we've talked about other substances where, for example, melting point is one of the parameters that's studied.

I can't speak as to why the manufacturer chose not to utilize melting point as part of their analysis with L-citrulline specifically.

DR. GULUR: Go ahead.

DR. BOGNER: May I follow up? So there are a number of places in the specification where the specification simply says "pass," but I don't know what the method is. There's no method description.

Can you comment on that? It's not as helpful to me, not understanding what method was used for a specification of pass.

DR. DAY: So the methodology oftentimes is not explicit on a certificate of analysis. The results are what's typically described. And they may have a range of acceptable results, such as for an assay, for example. Methodologies are oftentimes, as Dr. Davidson has pointed out, a component of the USP monograph. And for a substance such as this, the manufacturer would go through their own process of determining what is the appropriate methodology, and I can't speak to that.

Dr. Johnson might have some ideas.

DR. GULUR: Yes, Dr. Johnson?

DR. JOHNSON: Dr. Zhang, our quality chemist, is here and can answer questions about what is required to be on the CoA.

DR. ZHANG: This is Ben Zhang from OPQ. And usually, for characterization of the bulk substances, they will have the melting points. And

they're [indiscernible] results such as in MRs and IRS, all these techniques.

DR. GULUR: Any further questions or clarifications, Dr. Patel?

DR. PATEL: In terms of its place in therapy, under pharmacotherapy, you've mentioned standard of care. How does it compare to the alternatives that are available? I know the body of evidence, there weren't any comparative studies.

DR. JOHNSON: Some of it's a matter of convenience. When a patient is first diagnosed with hyperammonemia and the cause is unknown, the nitrogen scavengers are the first start to try to reduce the levels of pneumonia.

Then I believe that -- and Dr. Burman may want to comment additionally -- the next step when there's a diagnosis is the use of L-arginine. But that's an IV product, so they tend to switch to L-citrulline as fast as they can. Then obviously we have the one product for NAG, the specific match to the particular deficiency.

Does that answer the question that you were

looking for?

DR. PATEL: Yes. In addition to that, if L-citrulline were not to be available as an option, what's the next sequence?

DR. JOHNSON: I see what you're saying. And again, Dr. Burman may want to comment, but I believe that IV L-arginine would be the predominant therapy.

DR. GULUR: Dr. Burman?

DR. BURMAN: Thank you. We don't see many of these patients, and when we do, they're in consultation. But that is my understanding of the approach, and also L-citrulline is probably the most effective therapy.

DR. JOHNSON: I guess just to be clear, from FDA's viewpoint, our review didn't find another alternative for chronic oral use other than L-citrulline.

MS. DAVIDSON: If I could just comment, I think the logical conclusion to that would be that clinicians will be forced to use the dietary supplement, which is non-regulated and has been

found to be subpotent or completely absent in many products.

DR. GULUR: Thank you. The panel will now end the discussion, and we will start the vote. The panel will be using an electronic voting system for this meeting. Each voting member has three voting buttons on your microphone; yes, no, and abstain. Please vote by pressing your selection firmly. After everyone has voted, the vote will be complete.

The voting will be on the drug product just presented. This vote question relates to whether this product should be included on the 503A bulk list. After the completion of the vote, we will read the vote from the screen into the record and then hear individual comments from each member.

The question today is, FDA is proposing that L-citrulline for oral administration only be included on the 503A bulks list. Should L-citrulline for oral administration only be placed on the list? Please vote now.

(Voting.)

DR. GULUR: While we're waiting, I'll just repeat a few instructions. 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 monograph or component of an FDA-approved drug.

We will now summarize the vote as soon as we receive it. After you have made your selection, the light will continue to flash. If you're unsure of your vote, please press the corresponding button again.

(Pause.)

DR. CHEE: Sorry, everyone. Could everyone vote one more time, please?

DR. GULUR: Could all panel members please press the button one more time?

(Voting.)

DR. CHEE: For question 1 for L-citrulline, we have 12 yeses, zero no, and zero abstain.

DR. GULUR: We will now start with comments. Dr. Carome, if you would, get started.

DR. CAROME: Mike Carome. I voted yes. This was a pretty straightforward choice. I thought the drug was very well characterized. There are no significant safety concerns. It clearly has a definitive track record of being efficacious, and it's really the treatment of choice for these conditions. So that's why I voted yes.

DR. HOAG: I voted yes for all the reasons just mentioned. It seemed like a reasonable choice.

MS. JUNGMAN: Elizabeth Jungman. I voted yes because I thought the balance of factors that we're supposed to be considering supported the use, and I was influenced by the fact that it's the standard of care.

DR. BOGNER: Robin Bogner. I voted yes because the benefits clearly outweigh the risks.

DR. PATEL: I voted yes based on its safety and efficacy profile and the lack of many

alternatives to treat the disorder.

MR. HUMPHREY: William Humphrey. I voted yes for many of the same reasons already mentioned.

MS. DAVIDSON: Gigi Davidson. I voted yes because it is the standard of care, has been for many decades, and any safety signals apparently have come from use of unregulated products. So I strongly feel that this substance belongs in the triad between the prescriber and the pharmacist who can compound it very precisely.

DR. GULUR: Dr. Wall, would you like to comment?

DR. WALL: I voted yes for the reasons that my colleagues have mentioned. Thank you.

DR. GULUR: I'm Padma Gulur, and I voted yes for the same reasons. It's a stable substance, well characterized, 30 years of historical use, safe and efficacious, as has been demonstrated in these presentations.

DR. VAIDA: Allen Vaida. I voted yes for all the reasons that have been mentioned, but also because of the need for weight-based dosing.

DR. BURMAN: Ken Burman. I voted yes as well. These were nice presentations. This agent has important clinical uses, as we've heard. It is interesting there are no long-term clinical studies, which is unusual for the FDA, but in this circumstance seems appropriate. And I do think we need specific details on requirements for purity and impurities in the final product.

DR. GULUR: Dr. Venitz?

DR. VENITZ: This is Jurgen Venitz. I voted yes for pretty much the same reasons. What convinced me more than anything else was despite the absence of former clinical trials, the long history of use, and its part of standard of care.

DR. GULUR: Thank you. I'll just explain the no vote. Dr. Desai is not present. That is the one no vote.

Thank you, everyone. We will now have our morning break. Committee members, please remember that there should be no discussion of the meeting topic during the break, amongst yourselves, or with any members of the audience. Please return to your

seats in 10 minutes; 15 minutes. We've been given 15 minutes.

(Whereupon, at 9:28 a.m., a recess was taken.)

DR. GULUR: Welcome back, everyone. Before we begin, I will introduce one voting special government employee who will be participating in this topic for pregnenolone.

Dr. Jeff Fiedorowicz, would you please introduce yourself?

(No response.)

DR. GULUR: We will now have Dr. Harrouk present from the FDA.

FDA Presentation - Wafa Harrouk

DR. HARROUK: Good morning. My name is Wafa Harrouk. I'm a pharmacologist in the Office of Drug Evaluation IV, and I will be presenting to you the pregnenolone presentation and the FDA's review. First off, I would like to thank the review team who worked on this project, whose names are listed on this slide.

Pregnenolone has been nominated for

inclusion on the list of bulk drug substances for use in compounding under Section 503A of the FD&C Act. The proposed uses that we reviewed were those for the treatment of rheumatoid arthritis and hypercholesterolemia, and as an adjunctive therapy for schizophrenia and bipolar disorder.

The proposed routes of administration and dose ranges are oral capsules; 5 to 200-milligram, oral suspension, 10 to 200 milligram per mL; topical cream and gel, 1 to 20 percent; and injection suspension, 0.1 to 5 milligram per mL.

I should also note that pregnenolone is available in the U.S. as a dietary supplement in its oral form. It is also available in sprays and creams. Labeled claims vary and include support of hormones, memory, and brain, production of stress, improving skin and joints, anti-aging, and so on.

Next, I will present the physical and chemical characteristics of pregnenolone. Pregnenolone is an endogenous steroid. It is a well-characterized substance. It's insoluble in water and is likely to be stable under ordinary

storage conditions based on its chemical structure.

Besides its endogenous presence, pregnenolone can be synthesized by a process that involves hydrogenation of the starting material, 16-dehydro pregnenolone acetate followed by hydrolysis under basic conditions. Impurities may include residual starting materials or residual chemicals used in the synthesis process.

Next, I will discuss the general pharmacology of pregnenolone. As I mentioned earlier, pregnenolone is an endogenous steroid. It is derived from cholesterol and is a precursor for several steroid hormones, including reproductive hormones such as estrogens, progestins, and androgens, glucocorticoids, and mineral corticoids.

Among the downstream hormones lies dehydroepiandrosterone, which is the pre-cursor for 7-keto DHEA, which is the subject of another nomination, which will be discussed in the next presentation.

Collectively, these steroids act in concert to regulate critical body functions such as body

temperature, hormonal regulation, et cetera.

Pregnenolone is synthesized in the liver, skin, brain, retinal, reproductive organs, as well as in the peripheral nervous system. Disturbing the levels of pregnenolone impacts a number of downstream pathways. One of the most severe forms of this disturbance can result in congenital lipoid adrenal hyperplasia.

In terms of its non-clinical pharmacokinetics and toxicokinetics profile, we found that there were limited PK/TK data. However, the information that we found shows that the metabolic pathway of pregnenolone differs among species and amongst tissues where it is expressed.

For example, in rodents, pregnenolone is absorbed from the small intestines, where it undergoes extensive enterohepatic metabolism. It can cross the blood-brain barrier following intravenous and intranasal administration.

Several metabolites have been described for pregnenolone, and these include allopregnanolone, the sulfated and glucoronidated forms of

pregnenolone. Pregnenolone is mostly eliminated in the urine. And lastly, we did not find any toxicokinetic data for pregnenolone.

Moving on to the clinical pharmacokinetic profile for pregnenolone, we found limited human PK data. The available data suggests that orally administered pregnenolone is absorbed and metabolized in humans. A half-life of 5 to 25 hours was reported in a small study of three subjects.

In another study, it has been shown that pregnenolone blood level increased about fourfold after 12 weeks of administering pregnenolone compared to placebo. The study did not take subject's serum level out of the normal adult range for pregnenolone, so it didn't impact the endogenous levels of pregnenolone.

For dermal pharmacokinetics, we identified one study conducted in 10 post-menopausal women where pregnenolone was topically applied twice a day as a 3 percent facial cream for 4 months. Endogenous levels of pregnenolone showed a small

decrease in its level in response to the exogenously administered pregnenolone. We did not find any data on transdermal absorption in the small study.

Next, I will discuss the non-clinical safety profile for pregnenolone. We found a review article from the 1950s which reported a number of toxicity studies. Among these studies, there was one study where mice were given a single acute dose of up to 5 grams per kilogram body weight, and the author did not report any death in this study.

Other reported studies included oral gavage, oral feeding, intraperitoneal, and subcutaneous studies. None of these studies reported toxic effects for the elements that were measured, and I'll go into what elements were measured in these studies.

When pregnenolone was orally administered at 1 gram per kilogram in rats 3 times per week for 50 doses covering 17 weeks via oral and intraperitoneal route of administration, no significant toxicity findings were reported.

However, in this specific study, the measured endpoints were limited to blood parameters and organ weights.

In the feeding oral study, no change was seen in either the weight or food intake of the treated animals. In the subQ study, there were no changes in some of the organ weights that were chosen to be evaluated.

Overall the repeat dose toxicity profile for pregnenolone was not adequately designed to review the toxicity profile of pregnenolone. There were key elements, key parameters, such as body weight, clinical observations, gross examination, or histopathology of key organ systems that were not evaluated.

We did not find any studies for chronic toxicity, genotoxicity, developmental, or reproductive toxicity, or carcinogenicity. Overall, the available non-clinical toxicity data do not provide a well-understood safety program for pregnenolone to inform on its safety profiles in human.

Clinical adverse events will be discussed next. The first voluntary reporting system that we look at is the FDA adverse events reporting system, the FAERS. In the FAERS, we located seven reports. None of them were serious adverse events. Those adverse events that were self-reported included menopausal symptoms, dizziness, nausea, and excessive hair growth.

The CFSAN, the Center for Food, has their own reporting system, the CAERS, and that system reported included 30 reports, 18 of which reported a serious outcome that included 1 death and 17 hospitalizations or other serious events. The most commonly reported events included increase in heart rate, increase in blood pressure, dizziness, headache, pain, hypersensitivity, dyspnea, anxiety, tremor, and fatigue.

Causality in these two reporting systems, the FAERS and CAERS, cannot be established due to the use of multiple products or the use of products containing multiple ingredients.

Now, I'll discuss the safety events from

clinical trials. We found a few studies which reported systemic collection of adverse events in clinical trials. Some of these were small case series reported in the '50s, which involved intramuscular injection and/or oral ingestion up to doses of 600 milligrams daily for a variety of conditions, up to 8 weeks of dosing.

These case series reported a few cases of menorrhagia and weight gain, and a number of injection-site problems, which included abscesses that needed local excision and drainage. Whether the injection site reactions were caused by pregnenolone itself or other components of the formulations or the actual injection cannot be ruled out. We don't even have enough data on these 1950 reported studies.

In here also, adverse reactions that were seen included headache, decreased appetite, depression, and anxiety. And again, just like I talked about those side effects, adverse events for CAERS and FAERS, it's very hard to ascribe the conditions to whether it is the presence of

pregnenolone or other things that were done because we didn't have controlled studies.

More recently in the last decades, there have been studies reported in the literature which enrolled patients or subjects with psychiatric illnesses. These studies have not reported any significant safety signals. The dosing in the more recent studies were oral and ranged in dose between 50 milligrams to 500 milligrams daily.

I'll just mention one other safety piece of information, which is the State of California prohibits the sale of steroid precursors such as pregnenolone if certain warning statements are not included on the label. So pregnenolone is one of the ingredients that has to have a warning statement in the state of California. And a very important point to mention is that we did not find any long-term studies for pregnenolone.

In conclusion, in terms of safety, we have found insufficient data to support the safety profile of pregnenolone for treatment of chronic diseases that are the subject of this nominated

product. First of all, we had limited non-clinical data. Secondly, in terms of human, there are a few adverse events that were reported for pregnenolone and short-term clinical studies. No long-term safety studies were reported that support the use of pregnenolone in these chronic conditions.

Lastly, because of its role as a precursor in the production of more downstream key steroid hormones, a dose-related increase in adverse events -- some of them could be serious -- may occur with chronic administration of pregnenolone. We just don't know that piece of information.

Next, I will move on to discuss the effectiveness of pregnenolone for the nominated uses. Based on a literature search, we noticed that interest in developing pregnenolone as a treatment option for rheumatoid arthritis peaked in the 1950s.

We reviewed two uncontrolled case series which were submitted by the nominator where the dosing was up to 300 milligrams per day, and the duration was between 5 to 44 days of exposure to

pregnenolone. The results that have been reported show that some subjects improved, some worsened, and some did not have any effect either way.

The authors of these reports concluded that it was difficult to ascribe changes to pregnenolone, as any of the changes may have been caused by the normal spontaneous variation frequently seen in untreated cases of rheumatoid arthritis.

We also found two early controlled clinical trials also from the '50s by different authors where the dosing was from 10 to 150 days and the other study was 7 to 42 days. Neither study showed positive effects of pregnenolone on rheumatoid arthritis.

In summary, for the effectiveness of pregnenolone on rheumatoid arthritis, we found no evidence of effectiveness in this indication. And overall, we find that the studies were generally small uncontrolled case series, which is a study design that's problematic in a disease like RA with spontaneous remission and exacerbation of the

disease.

The next indication that we reviewed is hypercholesterolemia. In this regard, we found two uncontrolled retrospective chart reviews, where patients were treated with individually tailored anti-aging cocktail of 7 to 9 hormones at various doses, and pregnenolone was one of these hormones.

The problem with these two studies is that we didn't have control groups. There were several substances used, and both of these factors preclude us to deciding any effect on one of these substances, namely pregnenolone.

As I mentioned earlier, in more recent years, researchers have focused their effort on studying the effect of pregnenolone as an adjunctive therapy for cognition and other neurobehavioral diseases in a variety of mental health conditions.

The first one that was nominated was the use of pregnenolone as an adjunctive therapy for schizophrenia. In that regard, we found two exploratory trials. Each one was 8 weeks in

duration, which enrolled small numbers of subjects with schizophrenia or schizoaffective disorder and had multiple endpoints. There was no statistical correction for multiplicity, which is a design appropriate for generating hypothesis but not to really tease out any real effect of the drug.

One study used 6 instruments, and the other used 10 instruments. Both studies detected a trend in improvement in positive symptoms measured by the same subscale that the authors decided to use. However, one study only saw the trend in patients treated with the lowest dose, the 30-milligram per day, but not at the higher dose, the 200-milligram per day. The other study, the trend was seen in 8 subjects who are treated with pregnenolone at 500 milligrams per day.

There were also in the literature two larger placebo-controlled trials, and both of them failed to meet the primary prespecified endpoints that the authors chose. In the first trial, the researchers enrolled 120 subjects who were dosed with oral pregnenolone up to 500 milligrams per day. The

study did not show efficacy based on a prespecified co-primary outcomes, which included changes in cognition and functional capacity.

The other issue here, because this is in adjunctive therapy, the concomitant medication at baseline varied, and there were 19 subjects that had changes in their concomitant medication during the study. The authors concluded for these two studies that further investigation will be required to clarify the potential therapeutic role for pregnenolone in schizophrenia.

The second trial studied 82 patients with chronic schizophrenia. All patients were treated with the same concomitant medication in this trial. The patients in the pregnenolone arm received 50 milligrams per day of oral pregnenolone. The primary prespecified outcome was a change in the total positive and negative syndrome scale. However, again, the trial did not show a significant difference in PANSS scores between pregnenolone and placebo arms.

Overall, to summarize, the studies that we

found for the effect of pregnenolone as an adjunctive therapy for schizophrenia were inadequate to support the effectiveness claim.

The next indication is the use of pregnenolone as an adjunctive therapy for bipolar disorder. The nominators here submitted two articles reporting the results of small randomized placebo-controlled studies in patients with bipolar disorder who were given pregnenolone as adjunctive therapy to their conventional therapy.

The first exploratory study up-titrated dose in 70 subjects from 50 to 100 milligrams per day over 8 weeks' duration. This particular study used 6 different instruments and made no correction for multiplicity. The study had a large dropout rate, where more than half of the subjects dropped out of the study, and almost half of the subjects had changes in their primary therapy during the study.

Among the completers, which were only 18, pregnenolone-treated subjects showed a trend towards greater improvement in the Hamilton Rating Scale for Depression relative to placebo.

The second study also up-titrated pregnenolone from 50 to 500 milligrams per day over a 12-week period in 80 subjects. The primary outcome measure for this study was also the Hamilton Rating Scale for Depression. The results that we found on clinicaltrials.gov did not report a statistically significant change in that scale for pregnenolone subjects compared to placebo, although the numbers show a trend towards a greater improvement in the pregnenolone group compared to placebo.

In summary, for the use of pregnenolone as an adjunctive therapy for bipolar, although there were two studies that showed some promising trend in effectiveness and improving bipolar disease, there were a number of factors, including the change in concomitant therapies during the trial, the small subjects number, the statistical design issues, and other study-specific problems that precluded definitive conclusion. In both cases, the researchers called for further research into the effectiveness claims.

To pull together the effectiveness data that we reviewed, we found data for the various indications, however, we could not find data that supported the concept that pregnenolone is effective in treating rheumatoid arthritis or hypercholesterolemia. The data were inadequate to support that pregnenolone is an effective adjunctive therapy for schizophrenia or bipolar disorder.

Just a word here, all four conditions that I've been discussing are chronic conditions that can be serious depending on the severity and associated comorbidities that are seen in them. And lastly, there are numerous FDA-approved drug therapies for each of these nominated uses.

The last criterion that we evaluated was the historical use in compounding. A search of the literature on this matter shows that pregnenolone has been used in pharmacy compounding in the U.S. since at least 2003 and that its use has been wide in range and includes treatments for conditions such as aging, arthritis, endometriosis,

depression, hormone replacement, fatigue, lupus, multiple sclerosis, seizures, among other indications.

Just to remind the audience and the advisors, its use has been reported in Australia in compounded hormone replacement therapy. We did not find it to be listed in the British, European, or Japanese pharmacopoeias. And in the U.S., it is available as a dietary ingredient in dietary supplements, so it's available on the market.

In my big conclusion, what I hope I have conveyed during this presentation is that the evaluation of the four criterion for compounded drugs for pregnenolone were as follows.

We find that pregnenolone is a well-synthesized steroid; that its safety, both clinical and non-clinical, has not been adequately assessed; that its role as a precursor for other steroid hormones poses a potential increase in adverse events -- some of them could be serious -- that the lack of long-term safety data, the lack of efficacy data in the treatment of RA or cholesterolemia as

primary option, and as adjunct therapy for schizophrenia and bipolar diseases, that the historical use in compounding, which is widespread in the U.S. -- so we weighed all these.

We balanced all the four criteria, and based on that balancing, we do not recommend that pregnenolone be placed on the 503A list of compounding substances. With that, I'll close, and I'll entertain any questions. Thank you.

DR. GULUR: Before we move to the questions, Dr. Fiedorowicz, are you on the phone, and would you like to introduce yourself?

DR. FIEDOROWICZ: Can you hear me?

DR. GULUR: Yes.

DR. FIEDOROWICZ: Great. This is Jeff Fiedorowicz. I'm at the University of Iowa.

Clarifying Questions from the Committee

DR. GULUR: Thank you. At this time, we will accept clarifying questions from the committee. One of our first questions is from Dr. Venitz on the phone.

DR. VENITZ: The question is regarding

[indiscernible]. Could I get a clarification of that?

DR. GULUR: Dr. Venitz, could you please repeat? The connection is not very clear.

DR. CHEE: Dr. Venitz, I'll rephrase. So he's asking about the 50 percent dropout rate. Is that due to adverse events or lack of efficacy?

DR. HARROUK: It was not mentioned. It wasn't very specified. But I would like to see if Dr. Jean Kim is in the audience, if you would like to add anything to that study.

DR. KIM: I don't know -- [inaudible - off mic].

DR. HARROUK: I can get some more specific answers on that question. Whether it's because of safety or efficacy, I don't think it was very clarified, but we can look it up and get back to you.

DR. GULUR: Thank you.

Any other clarifying questions? Dr. Carome?

DR. CAROME: Mike Carome. So you mentioned that chronic long-term use of this drug, you worry

about certain adverse events occurring. Could you characterize the types of adverse events FDA might expect from this drug product with long-term use?

DR. HARROUK: Right. Because of its role as a steroid hormone and as a precursor, that's way up in the cascade of steroidogenesis. So adverse events that relate to hormone disturbances, things like I mentioned in the presentation, dysmenorrhea, for example, in post-menopausal women, headaches.

Let's see. What else did I have?

DR. FURLONG: Wafa, do you want me to try to tackle that a little bit?

DR. HARROUK: Yes.

DR. FURLONG: For full disclosure, I'm an obstetrician-gynecologist. I can speak to the downstream effects, estrogens and progestins, that are used even in what would be characterized as normal ranges. But we would also be concerned about mineralcorticoid imbalances or cortisol excess.

For example, with chronic – even, quote/unquote "normal" physiologic amounts of

estrogen in individuals, women can develop, for example, endometrial hyperplasia, endometrial cancers, venous thromboembolic events. These are long-term effects. These are usually not seen in short-term studies. Progestins we know are associated with, in the wrong population, breast cancers.

So even with endogenous hormones, there are potential carcinogenic effects. We don't have enough data to know with the pregnenolone. The range of normal for these hormones is huge. The body adjusts to external influences to achieve homeostasis and react in the moment to what is needed at that moment. Even excesses of cortisol, chronic long-term excesses of cortisol, can lead to Cushing's syndrome, Addison's disease, and so on.

In the short term, you're not going to pick up these sorts of complications. In a normal drug development program, which these don't undergo, of course, we would expect some long-term data to characterize those long-term effects.

DR. GULUR: Yes, Dr. Jungman?

MS. JUNGMAN: We received a number of comments about this product. Most of those really referenced its use as a hormone replacement therapy. So I'd appreciate if you'd speak just a moment about why FDA didn't evaluate it for that use.

DR. HARROUK: So I'll say a few words, and then I'll turn it over to Dr. Furlong. The way you review indications is by discussion with the nominators. We had the clarification e-mails between nominators, and hormone replacement therapy was not one of the indications that they sought out. That's the basic answer.

I don't know if Dr. Furlong has anything else to add.

DR. FURLONG: It was tough to figure out from the four initial nominations what we were really looking at here. Hormone therapy, I believe was one of the nominations' uses; pain, cognition. There were others as well. We didn't get any supportive information, and we couldn't find any supportive information. We know it's used for

hormone therapy. That might be its most common use, but we don't know. But there really isn't a lot of information out there in the literature about its use.

DR. GULUR: Dr. Braunstein?

DR. BRAUNSTEIN: Dr. Furlong, in terms of the rate-limiting step in corticosteroid hormone synthesis, is the transformation of cholesterol into pregnenolone, is that the rate-limiting step or is it downstream?

How is it regulated? Certainly, for example, hypercholesterolemia itself doesn't lead to -- I don't know. I'm not an expert in this. But I would think that that's not in and of itself what would lead to excesses in [indiscernible], or other sterile hormones.

Can you help us understand a little bit more about where the rate limiting -- how the control is, or where the control is in terms of the generation of the active hormones?

DR. FURLONG: I wish I could. I can't. I don't know enough about the subject to really be

able to address that question. Again, I'm an OB-GYN by training. I used to know a lot about estrogen regulation and progesterone regulation.

There are a lot of internal controls in the body. For example, estrogen is regulated in the brain - the hypothalamus, pituitary gland. It's also regulated in the end organs and the target organs. So there are feedback loops.

A woman's estrogen levels in the reproductive years are variable from day to day in the cycle, and the variation is over 200 orders of magnitude. So what's normal for pregnenolone, I really couldn't tell you what the rate-limiting step and the synthesis is. I don't know. Sorry.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: I had a really hard time sorting out the differences in pregnenolone and DHEA in terms of effect and what they do. But for the schizophrenia studies, it seems like they weren't able to sort out the adverse events from pregnenolone versus the conversion DHEA, which kind of goes along with a previous question about the

metabolic fate of it.

So that's one question. What were the adverse events from pregnenolone if any of the studies characterized that?

The other thought I had after reading the three studies is that there's a clear connection between lower pregnenolone serum levels in schizophrenic patients compared to normal patients, but that blood levels of DHEA were all over the map in all three studies, and they could not correlate that.

So again, it all goes back to metabolism and pregnenolone. To me, it seems like DHEA has more adverse events directly associated with it, but do we know how much pregnenolone goes to DHEA in schizophrenics?

DR. HARROUK: Before I answer that or we answer that question, pregnenolone, as I mentioned, in the PK, the pharmacokinetics of it, is that it is very rapidly absorbed, and it is transformed into its metabolites. So you have allopregnanolone, the sulfated and glucuronidated

forms of pregnenolone. So it doesn't stick around a lot, but obviously it sticks around long enough for it to turn on the cascade, the downstream cascades.

I was trying to get back to the big steroidogenesis graphs. But one of the paths that pregnenolone does when it goes down the pathway is three major pathways. Now, how much pregnenolone ends up in one, the hormone steroidal pathway or the glucocorticoids, or others, I didn't find any specific information on the pharmacology aspects of it to know what is the percentage that we can tell.

Now, in terms of the schizophrenic data, I'm not sure how much were the levels. So you're looking for the levels that the subjects with schizophrenia had for DHEA. Right? That's what you're looking for?

MS. DAVIDSON: I was trying to sort out how many adverse effects -- first of all, I couldn't really discern what were non-disease-related adverse effects in any of these studies, and if there were, were they attributable directly to

pregnenolone or to their metabolites.

DR. HARROUK: I think the authors in all of these, the adjunct use of pregnenolone in addition to the regular treatment could not be concluded. In all of these case-controlled studies, the authors ended up saying it could be the concomitant therapy. It could be pregnenolone.

So it doesn't help that the subjects had many other treatments that they're exposed to. And to squeeze out the effect, I guess they would have to have pregnenolone on the arm, but then these people have diseases that you're trying to control for. So I don't think I saw any information that teases out pregnenolone versus the other treatment options that were given.

MS. DAVIDSON: I didn't, either.

DR. HARROUK: Sorry. Yes.

MS. DAVIDSON: I just wanted to make sure I hadn't missed it.

I have one other question if you'll allow it.

DR. GULUR: Go ahead.

MS. DAVIDSON: This may be a question for the nominator presenters, but I noticed on the certificate of analysis that there were tests for pseudomonas, staph, salmonella, mold, coliforms, including E. coli, and yeast.

What is that all about? Is that from the synthesis of this? I did notice some of those on the C of A for citrulline, but I didn't mention it in that context. But I was very curious when I saw these on the C of A.

DR. HARROUK: I'm looking at our resident chemistry expert, Dr. Zhang. Basically, Dr. Giovanni [ph] found that, on the C of A, there were some mold and other things that have been specified on the C of A. Do you know what the source of these are or might be?

DR. ZHANG: I think, originally, the nomination mentioned it was a micronized form of the pregnenolone. And in this nomination, we're mainly focused on the drug substance itself. So the conclusion I think we draw from this review also applies to what they have [indiscernible].

MS. DAVIDSON: So you're suggesting that micronizing the substance contributes microbial or --

DR. ZHANG: We didn't see any difference in the review.

MS. DAVIDSON: I'm just curious, as I'm not used to seeing this information on substance C of As for chemicals, and I just wondered why.

DR. ZHANG: We don't usually see that either.

MS. DAVIDSON: Maybe that is a question for the presenter.

DR. HARROUK: So perhaps the next presentation, maybe can shed some light on that, too.

DR. JOHNSON: I think, then, just to add -- I'm sorry to interrupt --

DR. GULUR: Yes, please?

DR. JOHNSON: It can be fairly standard to assess the microbiology for a certificate of analysis; correct? That's the standard to make sure that there's not contamination in the

manufacturing process, not just in micronization, but in any handling.

MS. DAVIDSON: I'm just not used to seeing such a wide spectrum of microorganisms in the C of A, and I guess I was wondering when manufacturers of this dietary supplement make this, are they looking for the same things, or do we even know what the content of those microorganisms are in a dietary supplement since they're unregulated.

DR. JOHNSON: I'm sorry. Our chemistry colleagues were informing us that, oftentimes, if the bulk substance is to be used in intravenous products, then the surveillance of microbiological contamination is greater.

MS. DAVIDSON: In the antitoxic burden, sure.

DR. JOHNSON: I'm used to that. I'm sorry. I missed your other question.

MS. DAVIDSON: I was just wondering if the manufacturers of dietary supplements, for which I believe this is available, are aware of such contaminants and how would consumers or compounders

know, if they're starting with dietary supplements, what the burden is in those.

DR. JOHNSON: I don't think we have anyone here from CFSAN. Sometimes we have a representative to speak on dietary supplements, and I don't believe that we have anybody here. So I don't know that we know what the standard is.

MS. DAVIDSON: Okay. Thank you.

DR. GULUR: Thank you. We have a question on the phone from Dr. Wall, followed by Dr. Venitz, and then I'll get to Dr. Hoag. So Dr. Wall?

DR. WALL: I'm here, and my question has already just been asked. Thank you very much.

DR. GULUR: Dr. Venitz?

DR. VENITZ: My question is regarding the topical administration. Is that intended for topical use or is it intended for systemic absorption across the skin?

DR. HARROUK: So that study was the PK study that was done on post-menopausal women. And this was mostly for skin, removing wrinkles, et cetera. So the objective of that study was to see the

effect of pregnenolone and other things on the skin of post-menopausal women. And as a side arm of the study, they decided to measure how much was absorbed.

DR. GULUR: Dr. Venitz, did you wish to clarify further? Dr. Hoag?

DR. VENITZ: Thank you.

DR. HOAG: Steve Hoag. A quick comment. On this microbial testing, if it's a generic thing -- now, this is the product, but the USP has standard specifications and standard 1111 about what the microbial loads are and what bacteria should be there. But that's a product generally. I don't know about the C of A.

I had a question. You mentioned that this is used for injections as a suspension. I assume this is like IM and subcutaneous or more specification.

DR. HARROUK: Yes. So when we reviewed the articles that were submitted by the nominator and also what we found in the literature, some of the information that was submitted was that a

compounder could use it as an IM or subQ. The IM was then in the '50s for rheumatoid arthritis, but then a lot of the patients showed a sign of adverse events at the location, so they switched to oral. But, yes, so it's been used IM.

In terms of oral suspension, I don't know whether the compounders, they can speak on that later on, whether they actually do it routinely or not.

DR. FURLONG: Wafa, I just want to mention that we didn't see any recent articles, anything in the 2000s, where IM or IV formulations were used. The original nomination mentioned this. When we requested some clarification, what we got were two new uses and a dose range, but not a route of administration, so we went ahead and looked at the IM route of administration and what was available in the articles that had been submitted.

I don't see any evidence -- and Dr. Day will probably be able to clarify this -- that it's being used currently in parenteral formulations.

DR. HOAG: Yes. I just was wondering

because, sometimes, too, are they going to inject this into a joint or something like that?

DR. FURLONG: We don't think so, but I think we can ask the nominators.

DR. GULUR: Dr. Mixon?

MR. MIXON: In my 40 years of practice and 17 most recent years of full-time pharmacy compounding, I've never been asked to make a parenteral form of this drug.

DR. GULUR: Thank you.

DR. HARROUK: Thank you.

DR. GULUR: We now will proceed with the nominator presentations. We have one presentation, Dr. A.J. Day.

Nominator Presentation – A.J. Day

DR. DAY: Well, good morning again. As another introduction, my name is A.J. Day with PCCA. And to disclose conflict of interest, PCCA is a chemical wholesaler who does provide pregnenolone for use in compounding to community pharmacies.

So there were some really good questions

that were just brought up, so as we go through my presentation, I may pause a little bit and take time to address some of those questions, so the timing of some of the stuff. And hopefully the flow makes sense for all of this.

As was mentioned in the original nomination for pregnenolone, there were a number of utilizations that were proposed. And similar to the discussion with L-citrulline, we sought to clarify that when FDA contacted us in July of 2017 looking for specific clarification on the utilization of compounded pregnenolone.

At that time, we did specify that oral formulations are compounded as adjunctive therapy for positive/negative symptoms so on and so forth. And the clarification also was specific not to include the conditions of hypercholesterolemia or rheumatoid arthritis. So when we look at our presentation here, we will not address those indications.

As noted in the FDA briefing document, the FAERS and CAERS data noted that none of these

adverse events can be directly linked to the exclusive use of pregnenolone since all of the reported cases had other concomitant drugs and supplements, and that's again repeated in the CAERS data.

Again, FDA pointed out the Ritsner study in which all of these patients were taking concomitant medications for their disease and that no significant adverse events were observed throughout the duration of this study, of this trial.

Now, this slide, this topic came up in the discussion just now. One of the studies that is cited by FDA and was provided as a reference is from Marx from 2009. And the discussion was how much of this substance, of pregnenolone, leads to an increase in DHEA, leads to an increase in cortisol.

Now, while this was a small trial, they do address that very question, and they tested each of their subjects for increases in serum testosterone, free testosterone, cortisol, DHEA, estradiol, and androstenedione, and none of those levels increased

in the test subjects.

I actually reached out and spoke with Dr. Christine Marx at Duke University, and again, she operates within the confines of clinical trials. That's the limitation of her expertise and experience, however, she does note that she has not seen any adverse events in any of the patients for the various clinical trials that she's been conducting and had published since 2009, including those that are ongoing right now.

Again, more safety data from that same 2009 article, they talk about the studies going up to 500 milligrams per day, going back to the 1950s. Some of those were utilizing injection methodologies. Those are not what is currently being compounded for.

This was an 8-week trial, and during the 8 weeks of treatment -- and all of this information was reported to FDA because it's being conducted under an IND. So while the reported data may be a little bit limited within the trial that's been published, FDA should have access to all of the

adverse event data for all of the different patients involved in that IND. And I think it's important to note that none of that was mentioned as a significant safety signal in the FDA's presentation.

In 2011, Dr. Marx also published another study, and they looked at -- the only adverse event reported from any of those subjects was erythema in one male following an oral dose of 50 milligrams a day. No significant safety signals were reported from trials in schizophrenic or bipolar patients where pregnenolone was used as adjunctive therapy to FDA-approved drugs. This is from the FDA briefing document.

So we have a series of studies that have been shown as evidence for the clinical utilization of pregnenolone in the psychiatric disorders. The majority of these trials is 8 weeks with one of the trials lasting 12 weeks.

In the Marx 2014 study, they note that safety data was collected at each visit. And, again, this was also conducted under an IND. So

all of that data, individual patient safety data, should be on file with FDA. And none of that was reported as a safety signal.

Now, before I get to this next slide, let me also point out that there was some discussion about the dropout rates and what might be attributing to that.

Dropout rates in placebo-controlled and active-controlled clinical trials of anti-psychotic drugs, a meta-analysis; this is an article that was published in 2005, and it's specifically looking at anti-psychotic therapies and high rates of patient dropouts in the clinical trials, even the trials that are used for seeking FDA approval.

This was a study selection that looked at double-blind, randomized, controlled trials. The author on it, last name is Kemmler, Archives of General Psychiatry. And they're looking at randomized controlled clinical trials of second-generation anti-psychotics risperidone, olanzapine, quetiapine, and a few others. I won't read you the whole thing.

The conclusion was that the use of placebo-controlled design had a major effect on the dropout rates observed, because high dropout rates affect the generalizability of such studies. It is suggested that, in addition to the placebo-controlled trials, studies with alternative designs need to be considered when evaluating an anti-psychotic's clinical profile.

This is just to talk about some of the limitations when we're dealing with patient population that is very difficult to keep compliant with their medications.

There have been further studies. This is from the Journal of Biological Psychiatry from 1994, talking about the CSF neural active steroids in affective disorders, pregnenolone, progesterone, and DBI. In the conclusion of this study, they mentioned that CSF pregnenolone is decreased in subjects with affective illness, particularly during episodes of active depression.

So here we have a little bit more data on the natural biological impact of these hormone

pathways in psychiatric disorders.

One thing that I wanted to understand is, when FDA talks about limitations on the data that is available, what kind of expectation should we have for this? What's the standard of care? What's the standard of analysis?

So I chose two of the more recently approved FDA anti-psychotics. This information is publicly available. You have the URL on your screen. In the FDA approval documentation for the NDA for ziprasidone, for example, they concluded that 3 out of 4 short-term -- that were 4 to 6 weeks -- fixed-dose placebo-controlled trials showed superior efficacy of ziprasidone over placebo. Then in addition to that, they had one study that was 52 weeks that was not an active control study, but was just placebo controlled.

So the clinical efficacy of this drug was determined from 3 out of 4 short-term trials, 2 of them lasting 4 weeks, 2 of them lasting 6 weeks. One of them did not show superior efficacy of ziprasidone, yet the drug was still approved. The

clinical efficacy was based off of those short-term trials. And here, you've seen a series of trials that were 8 to 12 weeks for pregnenolone.

I'd also note that pregnenolone is not an item that's going to be patentable and not going to have market exclusivity. So the motivation, the return on investment for a sponsor to conduct such large-scale clinical trials is markedly different from what you're looking at with ziprasidone.

Again, looking at the next drug, quetiapine, three short-term 6-week controlled trials on inpatients. None of these were ambulatory patients, patients in a community setting, for which compliance is a much more significant issue and keeping them to be on that regimen. The adolescent approval for quetiapine is demonstrated based off of a single 6-week double-blind placebo-controlled trial.

Looking at the level of evidence, looking at the bar that we set in how we accepted the type of data for the type of patients that we're looking at must be kept into perspective. So this discussion

about there being multiple FDA-approved products indicated to treat these conditions proposed suggests that the products that are out there are both safe and effective for the patients that we're seeing. And we know that, in reality, we're not adequately taking care of the mental health of these patients for both bipolar disorders as well as the general schizophrenic patients.

From the Journal of Clinical Psychiatry, we have an article talking about concerns about these adverse events have been replaced by concerns about metabolic side effects.

One of the challenges with this particular meeting today is the level of short notice. So we've got a holiday week and we had three weeks notice about both the actual meeting and what was going to get be discussed.

As such, we spoke with a number of psychiatrists about their clinical utilization of pregnenolone as a component of therapy, and a few of them wanted to be here, but could not rearrange their patient care schedules to be here. And one

of them was able to provide me with some comments, which I'd like to read to you now.

"My name is Dr. Elizabeth Stuller. I'm an American Board of Psychiatry and neurology double board-certified adult and addiction psychiatrist. During the course of each year, I have practiced in private and public hospital psychiatry, working within the inner city, middle class, and rich subgroups of our American population. As a result, I have been witness to both traditional and integrative models of medicine, pharmaceutical access, and insurance access in all sectors.

"In the addiction psychiatry field, my patients are very complex, with multiple morbidities and mortalities. The inner-city population patient is often on 3 to 5 substances of abuse or dependence, namely alcohol, tobacco, cannabis, and often crack cocaine, and heroin. They often have an impaired hepatic metabolism secondary to hepatitis C or immune dysfunction secondary to HIV.

"They often have comorbid medical conditions

such as hypertension, hypercholesterolemia, obesity, and taking multiple medications for these conditions. The stable diet of the inner city is mainly cereal and milk.

"In private practice, I see both middle class and wealthy patients often with secretive alcohol, amphetamine, and cannabis use and more economical access to designer drugs such as ecstasy, K-2, and Spice, which are cannabis synthetics known to induce psychosis.

"The rich have better access to better prescription drugs and are often plagued with opioid dependence and better, faster internet access to overseas internet clandestine chemistry.

"Patients with severe mental illness such as schizophrenia have a reduced life expectancy compared to the general population. They have a two- to threefold increased risk of dying and this mortality gap associated with mental illness, compared to the general population, has widened in recent years. People with severe mental illness have nearly twice the normal risk of dying from

cardiovascular disease and are more likely to be overweight, smoke, have diabetes, hypertension, and dyslipidemias.

"Schizophrenia is an incredibly complex disorder that has increasingly been recognized as having multi-factorial etiologies and increasingly being viewed from a developmental perspective per the National Institute of Health, although its prevalence is only 1.1 percent of the U.S. population.

"Schizophrenia can affect children and adults and often occurs in the late teens. Although there are many FDA-approved anti-psychotic medications to treat schizophrenia, as noted in your FDA report, these medications present their own risks, including a significant risk of metabolic syndrome.

"Over recent years, research shows that anti-psychotics can have a negative impact on traditional modifiable risk factors. In a systemic review of the literature, since 2003, identified in PubMed, using metabolic syndrome, anti-psychotics,

schizophrenia, and psychotic disorders, prevalence and incidence of metabolic syndrome, including comparison of different ethnic groups, show a direct correlation secondary to the use of anti-psychotic medications.

"Additionally, despite the advances in our anti-psychotic medications, the total clinical response remains insufficient. When response to anti-psychotics is inadequate, augmentation strategies are often implemented.

"Additional barriers in our patient population with severe mental illness and addiction includes increased incidence of medication non-adherence, incident likelihood of discontinuing treatment, increased difficulty in recruiting and retaining subject for long-term research trials due to chaotic lifestyles, and financial barriers and decreased access to healthcare.

"Therefore, I would like to present a more practical clinical view of the FDA's review concerning pregnenolone. Pregnenolone is considered a neurosteroid that is naturally

produced in the brain, adrenal glands, and gonads. Pregnenolone acts as a signaling molecule for neocortical organization during brain development and has extremely important neuromodulating effects on the GABA-A and MDA signal 1 cholinergic and dopamine symptoms.

"Pregnenolone helps to regulate the growth of neurons and cerebral brain-derived neurotrophic factor levels, enhances myelination and synaptogenesis, and is considered to have neuroprotective properties.

"Ongoing clinical evidence suggests that pregnenolone and its metabolites are involved in this pathophysiology of schizophrenia, mood disorders, dementia, and substance abuse. Low circulating levels of pregnenolone has also been correlated in elderly patients with dementia, patients with major depression, anxiety disorders, and in chronically medicated schizophrenic patients.

"According to the FDA report I reviewed, the FDA adverse event reporting system, reviews from

January 2000 to June 2017 showed that no adverse events could be directly linked to the exclusive use of pregnenolone. The CFSAN report, which collects reports for adverse events involving food, cosmetics, and dietary supplements, concluded that adverse events in the multi-ingredient reports could not be attributed to pregnenolone.

"No significant safety signals were reported from trials of schizophrenic or bipolar patients, where pregnenolone was used as an adjunctive therapy to FDA-approved drugs, yet FDA concluded that we do not find clinical safety of pregnenolone adequately supported.

"In the Ritsner study of 2011, in which pregnenolone was used as an adjunct medication for schizophrenic and schizoaffective patients, no significant adverse events were observed. As noted earlier, a barrier in psychiatric studies, for example, as the schizophrenic prevalence in the U.S. is only 1.1 percent, smaller sample sizes should be expected.

"With a retention rate of about 76 percent

in the 2011 Ritsner study, given the difficulty of patient retention in schizophrenic research trials, I would consider this a credible study. Additionally, many mentally ill patients tend to somatize their mental illness, and, again, no significant adverse events should be considered an important report, given the difficulties with our patient population."

Dr. Stuller goes on to cite numerous clinical trials of anti-psychotic drugs with dropout rates of 33 percent to 50 percent. And these high dropout rates give rise to considerable problems concerning the generalizability of results obtained from the randomized clinical trials.

As patient retention continues to be a barrier to treatment, other 8-week study by Dr. Kardashev, adjunct pregnenolone with L-theanine was shown to relieve both negative and anxiety symptoms in schizophrenia and schizoaffective disorders. Adjuncts which improve both negative symptoms and patient retention should be of great value and not readily abandoned by the FDA.

Now, Dr. Stuller wanted to be here to present. When we asked if she would be able to call in for the meeting, participate via phone call, we were instructed that, no; all of the nominator presentations must be in person.

This is particularly disappointing knowing that we have three voting members of the committee who are participating by phone today. Had she been able to be on the phone, I'm sure she would have loved to answer any questions you have about material that I just read to you.

Again, there are more instances of harm from FDA-approved medications. This is all published literature, even as recently as January of this year, treatment failure. Psychosis relapse was the most frequent outcome in the most key studies, ranging from 38 to 93 percent in some of these clinical trials, high rates of concomitant medications to manage these drug adverse events.

So you have patients who are receiving these FDA-approved anti-psychotics, and to manage the adverse events, they're taking multiple concomitant

medications. It becomes a snowball effect, and the financial burden on these patients contributes to their lack of compliance with their medication therapy.

These are some of the key points addressed from that specific article; treatment failure the most frequent outcome.

This was a post by the former NIMH director, Thomas Insel, on the anti-psychotics. "We realize that for too many people, today's treatments are not good enough. A hundred years after defining the disorder and 50 years after breakthrough medications, we still have much to learn."

In terms of some information about the source of pregnenolone that we utilize in compounding, we do get it from an FDA-registered and inspected CGMP facility. Regarding the presence of some of the information on the certificate of analysis, the microbial information is pretty standard. We have that on lots of different chemicals regardless of its intended use as a sterile product or oral non-sterile and

anything of that nature. Oftentimes, these are simply being compliant with USP chapter 61 and 62, I believe.

Hopefully, I've addressed a few of the discussion points that also came up previously, and if there are questions, I'm happy to stick around.

Clarifying Questions from the Committee

DR. GULUR: We will now accept clarifying questions.

DR. GANLEY: I just want to clarify one point. Dr. Day had suggested we can go into an IND, and look at it, and present the information. At this meeting, we're not able to, just as you were limited to what's available in the public domain.

The other thing is, I would suggest Dr. Stuller submit the comments to the public docket for this and any other information she wants to do. And just to clarify some things you'd mentioned about ziprasidone, I'm just looking into the package insert, because you inferred that there was only about 300 long-term patients studied.

It says in the package insert, clinical trials for oral ziprasidone included approximately 5700 patients and/or normal subjects exposed to 1 or more doses of ziprasidone. Of these 5700, over 4800 were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 1831 patient-years.

I could go on and list it. So I just want to be clear that the information that was presented by Dr. Day isn't the complete information for ziprasidone. There's a lot of information on ziprasidone.

DR. GULUR: Dr. Day, I do have a question similarly. You had mentioned in the FDA products, the two products that you had mentioned, which were approved with short-term clinical efficacy trials, what were the safety durations that they looked at? Were they also 8 weeks? Did they look at those? And if the FDA has more information, they could share it as well.

DR. DAY: The safety trial I believe on ziprasidone was 52 weeks. On quetiapine, I did not

see that information on the link that I had access to.

DR. GULUR: Another question I have is that you've quoted Christine Marx's article from 2009. She has a subsequent article in 2011, I believe. Have you had a chance to review that as well?

DR. DAY: I have.

DR. GULUR: She concludes by saying, "Future efforts and larger cohorts will be required to investigate pregnenolone as a possible therapeutic candidate in schizophrenia. Early efforts are promising, but merit further investigation." And this was a 2011 article that's there.

DR. DAY: Correct.

DR. GULUR: So I guess my clarifying question is how do we come to the conclusion that she found this effective for schizophrenia or was recommending it for that?

DR. DAY: So Dr. Marx continues to be engaged with clinical trials utilizing pregnenolone, and her field is clinical trials. She does not operate outside of a clinical trial

setting for pregnenolone and does not recommend it outside of the clinical trials; although she does understand that, clinically and in practice and community settings, in particular, that psychiatrists have been recommending pregnenolone supplements for their patients for a number of years, and she does not have any concerns about the safety signaling or potential adjunctive efficacy of it.

As you will see in nearly every clinical trial you will review, the conclusion typically does say that more studies are needed. That is particularly noticeable, given the scale of the studies on pregnenolone.

So while the studies are notably small in scope, the safety profile, the fact that it is an endogenous hormone, when we look at some of the discussions on potential downstream effects that talked about the 2009 Marx study, where she actually looked at serum levels of some of those downstream hormones, we have two FDA-approved products that are in that hormone cascade.

Oral progesterone is the very next metabolic byproduct of pregnenolone, so any concerns about the increase in cortisol and other sex hormones would be also likely more noticeable with the manufactured product of oral progesterone capsule because it's going through the same metabolic pathways. We also have now a newly FDA-approved vaginal product for DHEA. So there's also safety data on the downstream metabolic products of DHEA supplementation.

Part of the reason that we feel that this substance would be best available for patients through compounding is because of potential side effects, because of its role as a steroid hormone, as a hormone precursor. We feel that needs to be in a patient's chart. There needs to be adequate patient consultations with that, and that's the process that undergoes compounding medications.

So you can have a thorough review as well as adverse event counseling and monitoring within the triad of care, with your physician, the patient, and the pharmacist. When it's available solely as

a dietary supplement, you lose that.

You may have a teenager working in a supplement store who really has no education or knowledge about those adverse events, and we really hope that a substance such as pregnenolone can be available for the patients who need it, but with proper and appropriate oversight. And that's where having it approved and custom made by pharmacists seems to be more appropriate than the dietary supplement alternative.

DR. GULUR: Thank you. I have one further question. Are you familiar with the paper of the randomized double-blind placebo-controlled trial of pregnenolone for bipolar depression? That's a 2014 article by Brown, et al.

DR. DAY: Yes.

DR. GULUR: In that article, they conclude or in their discussion say that orally administered pregnenolone has a complicated metabolism and may not be the most efficient method of increasing levels of pregnenolone and other neuroactive steroids in the brain.

In fact, they go further to say, in the future, synthetic, which is viral gene delivery, approaches should be considered. Could you comment on that?

DR. DAY: Yes. I think some of that supports what Marx found in her 2009 study, that you're not necessarily increasing your downstream hormone production, whether it's cortisol, or DHEA, or testosterone from orally administered pregnenolone. The effect on behavioral modifications for these specific schizophrenic or bipolar patients is not necessarily attributable to those downstream hormone production effects.

DR. GULUR: So what is it attributable to?

DR. DAY: I can't say with certainty. I think that's the purpose of some of these clinical trials, but I believe that what we're seeing, as FDA noted, is that there's a consistent trend towards an effect being produced.

DR. GULUR: Any further clarifying questions? We have Dr. Wall on the phone who has a question.

DR. WALL: Thank you very much. A question for you, and you sort of brought it up yourself. But you talked about patients need to be appropriately counseled when you're looking at medications.

Can you please share what is currently, in your experience, the routine counseling and sharing of what adverse events are possible and side effects patients may see when you're using these drugs for really long-term, chronic use?

DR. DAY: So in terms of the potential adverse events, I believe that was something that was addressed in the FDA's round of discussion. And of note, I feel like a lot of those were adverse event profiles from FDA-approved progestins and synthetics, so conjugated estrogens, and esterified estrogens, and synthetic progestins as opposed to the molecules that we're talking about here, which their structure is not as a synthetic. It's an identical chemical structure to what our body produces endogenously.

So the downstream effects could potentially

be, as was mentioned, everything from elevated cortisol type of effects from endogenously produced. And there are negative feedback loops, as was talked about, for maintaining homeostasis from the endogenous production versus exogenously supplemented hormones.

But the patient counseling has to do with everything from your typical sex hormone supplementation, so your night sweats and hot flashes, to some of your more cortisol-derived adverse events.

DR. WALL: So would you say that those things are routinely being discussed with the patients and they are routinely being monitored by that front-line pharmacist who is taking care of them?

DR. DAY: They should be, and I would argue that, yes, they are, but I cannot state that definitively because I'm not necessarily the one dispensing and interacting with those patients.

DR. WALL: Thank you.

DR. GULUR: Dr. Mixon?

MR. MIXON: Is it appropriate for me to respond to Dr. Wall's question?

DR. GULUR: Yes

MR. MIXON: The likelihood that patient-focused conversation is going to occur is much more likely with a compounded preparation than it is with somebody just going to Walmart and buying a bottle of a supplement off the shelf, which I just want to remind everybody, this drug is widely available in the over-the-counter market.

DR. GULUR: Dr. Furlong?

DR. FURLONG: I just wanted to make a clarification. There are FDA-approved estradiol and progesterone products, so although there are a lot of synthetics, synthetics are usually modified, for example, so that they're better absorbed orally.

Every FDA-approved product, we know, with each approved product, whether they're generic or new drugs, how much of the actual active ingredient is delivered and at what rate that required a study pre-marketing.

Open Public Hearing

DR. GULUR: Thank you, Dr. Day.

We will now proceed to hear open public hearing speakers. I will read the following OPH statement into the record.

Both the Food and Drug Administration and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency of the open public hearing session of the advisory committee meeting, FDA believes 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 a sponsor, its 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 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. Therefore, please speak only when recognized by the chair. Thank you for your cooperation.

Will the open public hearing speaker number 1 step up to the podium?

COL JOHNSON: Good morning. I want to first-off wish everyone a happy Thanksgiving as we go into our Thanksgiving week. I want to thank the PCAC for this opportunity, FDA, and members of the gallery as well.

My name is Colonel Air Force Retired Jeffrey A. Johnson. I am a compounding pharmacist that has been compounding as a pharmacist for over 40 years, 30 years in the military. I am a paid consultant with MEDISCA, and I am here on that behalf.

As far as what we're looking at today, I'm really just going to kind of foot-stomp a couple of things that caught my attention as Dr. Day was sharing his -- and give me a second while I get back to my notes. Thank you.

I think what I really want to focus on is that it hit me there were four specific things that really, I think, he highlighted very well. The FDA's presentation was very, very good. But I really think that there's an issue that we need to be cognizant of, is that sometimes we have a tendency with some of the smaller studies to just

consider that they're not relevant. And that's not true because they are relevant, and I think we have to keep that in mind.

As he pointed out very, very well, that the level of evidence -- we just need to keep in mind that we need to be balanced as we use that in our consideration. It is good when you have a study that has a lot of patients in it, multiple arms that you can go back and look at. But to say that a study is insignificant if it only had, say, 50 patients, I'm not sure we can do that.

Also, I think that sometimes it gets a little distressing as a practicing pharmacist and a practicing compounding pharmacist, that it seems like there is a generic shield that gets thrown up that there's multiple FDA-approved prescriptions for that therapy and that a dietary supplement is available instead of the compound.

I am going to be speaking later on resveratrol, and I have a slide that will deal with that at that point. But I think there are some really important things. One was made by one of

our PCAC members that having a compounding pharmacist that has done that, you can be assured of the quality and the purity, and that they are going to be doing that counseling at a very, very high rate and a very high level of intensity with that patient. Talking about the triad between the patient, the pharmacist, and provider, that's what a compounding pharmacist offers in that situation.

Then again, going back to the adequate support, I do think that, if you take all those studies into account, there is adequate support to what PCCA is saying as far as pregnenolone.

That's really all I have at this point. I'm open to any questions.

DR. GULUR: Any questions for the committee members?

(No response.)

DR. GULUR: Thank you very much.

COL JOHNSON: Thank you, ma'am.

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

now begin the panel discussion on pregnenolone. Any comments from our committee members, Dr. Braunstein?

DR. BRAUNSTEIN: So I'm going to direct this at FDA, and I'm a little torn betwixt and between on this one. But given 21st-century cures and a disease where there is a great unmet need, current therapies are inadequate, how do we justify taking something out of the hands of physicians and patients when it's not clearly a highly toxic substance?

DR. FURLONG: I may have to call on my help line here. Dr. Kim, I don't know if you have any thoughts on it, and we have a couple of psychiatrists here. This will not affect its availability as a dietary supplement. I think you should be aware of that, and physicians can still use it or recommend it if they wish.

The dietary supplement dose ranges are within the ranges that are described in the nomination, but let me just defer to Dr. Kim.

DR. KIM: Yes. Just to agree with

Dr. Furlong, it's still going to be available. The issue is, when we approve a drug for use in the general public, it has to be shown to be both effective and safe. And the bar for evidence in terms of showing that this drug works for the intended use in schizophrenia and bipolar has not been met.

DR. BRAUNSTEIN: I just want to follow up on that because my understanding is that there is no positive list of drugs that the FDA states has been proven to be safe and effective. Right?

Is that what this list is intended -- when we put a drug on the list, are we actually saying that it's proven to be safe and effective or that it simply can be used in compounding?

MS. BORMEL: No, we're not saying that. The standard for the bulks list is not the same as that of an FDA-approved drug. When we're looking at the bulks list, we're looking at all the criteria that we've set out and making an assessment based on balancing those criteria. So that is what our reviewers have done.

Remember that once we make a decision at the advisory committee, still the bulk substances have to be proposed in the Federal Register notice as a proposed rulemaking, and we would get comments for that, just to give you the whole process. But the standard, you're correct, is not the same as -- the standard for putting drugs on the 503A bulks list is not the same standard as an FDA-approved drug.

DR. KIM: Right. I guess I'm speaking more regarding to the existing therapies that have been approved, not necessarily the bulk ones.

DR. GULUR: Dr. Mixon?

MR. MIXON: We know that treating patients with rare diseases or uncommon condition, or rare conditions, is not a perfect science. This is why physicians prescribe compounding medications and pharmacists prepare them.

We can't begin to predict all the circumstances where something may need to be compounded. To me, it's very imperfect to take a dietary substance off the shelf to use in a compounded medication. I would much rather have

the pure active ingredient, where I have the certificate of analysis and can review it and compare it to standards.

First of all, if I had a vote on this committee, I would vote to have this drug or not restrict its use in compounding. Second of all, I'd just ask that the committee understand that this is one tool that we have in our toolbox. Physicians can prescribe it. We can compound it.

I would ask that that be maintained because we can't predict. We're talking about people with rare conditions sometimes. Many times, it's to balance hormones. It's just another tool that we need, and there's no reason not to allow it to be used, in my opinion.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: Is there any evidence about the quality of the pregnenolone dietary supplements? There was obviously a quality signal with L-citrulline, but are there any reports? I searched prior to the meeting, and I couldn't find anything specific. But I wondered if there had

been problems with these dietary supplements. I know the California warning is in effect, but I think that's in general for steroid precursors.

DR. FURLONG: We didn't find anything in the CAERS database, and we don't have anyone from CFSAN here who could discuss that.

MS. BORMEL: We do have someone from CFSAN here.

DR. WELCH: My name is Kara Welsh. I'm from Office of Dietary Supplement Programs at CFSAN. We don't necessarily have a picture of the quality of the dietary supplements that are currently on the market.

There are requirements, manufacturing requirements, labeling and safety requirements, and they're confirmed by regular inspections by FDA personnel, but there isn't necessarily a barrier to market that they have to proactively come to FDA before getting their products, putting their products on the market?

MS. DAVIDSON: Can I ask you one more question? So is it possible that an on-the-shelf

dietary supplement of pregnenolone could contain some of the metabolites that are definitely connected to the adverse events.

DR. WELCH: Certainly always a possibility. They do have requirements, manufacturing requirements, the good manufacturing practice requirements. They do have to meet identity, purity, strength, composition, and limits on those types of contaminants that may adulterate the finished product. Those are all finished product specifications.

So those are requirements established by CGMPs. They are confirmed if a facility is inspected, but again, we don't necessarily get those reports in advance of a product going on the market.

MS. DAVIDSON: Just to clarify, that is for dietary supplements as well as approved products?

DR. WELCH: I am only speaking about dietary supplements.

MS. DAVIDSON: Okay.

DR. FURLONG: I would like to clarify,

though, that that's also true of compounded products. We don't do a pre-marketing review of compounded products or dietary supplements. We do a pre-marketing review of approved new drugs, engineered products.

MS. DAVIDSON: And the only difference being that compounds are prescription only, and dietary supplements pretty much drop off the therapeutic radar if people just go buy them off the shelf.

DR. FURLONG: That's correct. Yes.

DR. GULUR: Dr. Hoag?

DR. HOAG: Maybe a question and a comment. One thing with the DSHEA, it depends what's claimed on the bottle because they have all those CGMPs, but they may not claim that there's a dissolution rate, and this drug with a low solubility, if it's not micronized or something. But it would still meet the requirements, but it may not perform as a drug product because they don't claim it that way.

DR. WELCH: The labelings are different than the CGMP requirements. You're right.

DR. HOAG: So if they don't make a claim,

there's no requirement to meet that.

DR. WELCH: There is a requirement in the good manufacturing practices separate from the labeling requirements. They don't have to put it on the label, that it has -- they don't necessarily have to put all of the contaminants and all of the exact purity on the label or the dissolution requirements, but in their internal documentation, the CGMP documentation, they do need to have identity, purity, strength, composition, and limits on contaminants. They have to have a specification and testing methodology that they've met those specifications for finished products.

DR. HOAG: Yes, because I think those all have to do with the safety, but do they have to do with the performance of the product in terms of a drug product?

DR. WELCH: Well, I'm only speaking to dietary supplements, but many manufacturers do have those performance requirements as specifications and establish them as well as demonstrate that they've met them in their CGMP documentation.

DR. HOAG: But that may or may not be a requirement, as I understand it.

DR. WELCH: Thinking specifically, dissolution isn't necessarily a predetermined requirement. It's not written into the dietary supplement CGMPs, but it is a commonly found specification and verification.

DR. HOAG: But it's hard for a patient to know whether that was a requirement unless they claim it on the bottle.

DR. WELCH: Correct.

DR. HOAG: Then my question actually was, how does the dietary supplement requirements compare to this list of compounding? Are there differences, the same requirements, different? What are the differences between these two lists?

DR. WELCH: I think someone from the table should probably answer that first.

DR. FURLONG: Yes. I don't have any particular expertise in nutritional supplements. I can say that in both spaces, though, there is no pre-marketing review, and we're not putting on the

market particular products that have been assessed for delivery, bioequivalence, or even bioavailability.

You don't know when you're purchasing these, either drugs or nutritional supplements, how much of the ingredient is actually bioavailable to the patient.

DR. WELCH: Then from the dietary supplement perspective, FDA is largely focused on the safety and the quality of the products, safety first and foremost, the quality specifically related to the CGMP requirements, labeling requirements. But they are considered a category of food, so largely on safety, not on efficacy.

DR. GULUR: Dr. Ganley?

DR. GANLEY: Yes. I just want to clarify that by the way the question was asked, that there are certain requirements on compounded drugs to show these things, and they're not. They're not required to be manufactured under good manufacturing practices.

They have to follow chapter 795 in USP for

compounding non-sterile products. And I don't recall there being any issue or any requirement in there that they have to do dissolution testing or solubility testing of those products.

So to suggest otherwise is just not accurate because we don't know. Someone could create a tablet that's much harder and is not going to dissolve, but there's not a requirement that they actually do the testing on that.

DR. DOHM: I would just briefly add to that, that the requirements of USP are going to be dependent on state law. So whether or not the state law imposes the requirement that you have to comply with, USP 795 or otherwise, will vary.

DR. GULUR: I'd like to reach out to the members on the phone. Dr. Fiedorowicz, do you have any comments for this discussion?

DR. FIEDOROWICZ: I don't have any comments at this time, but I would like some clarity from the FDA about how to balance the four criteria or if there's any precedence on balancing them.

DR. DOHM: I think I might need a little

help with the question. So obviously, in terms of balancing, it's a balancing test, so each factor will be weighed in one way or another in a given situation. As for precedent, obviously this is the eighth advisory committee meeting, so we have many examples of where we've found things in various ways over the years.

So is there something in particular you are asking for guidance about in terms of the balancing or a particular precedent you might be looking for, such as a situation where we have potential safety concerns about chronic use, and not very good evidence of effectiveness, and how we've weighed that in the past?

DR. FIEDOROWICZ: That would be helpful.

DR. DOHM: I'd have to look back at particular substances, but I believe in the past, we have looked at safety concerns associated with chronic use and situations in which there's little to no effectiveness evidence, and then also some historical use in compounding and very relatively few concerns about physical and chemical

characteristics and advised against putting it on the list.

Is that fair to say? Yes, others are nodding.

DR. FIEDOROWICZ: Thank you.

DR. GULUR: Dr. Venitz, you had a question?

DR. VENITZ: Yes. This is a clarification question for the FDA. I understand from Dr. Day's presentation that there's an IND ongoing with the drug of interest, and I understand that you can't give us any information about what's actually going on with the IND, so let me ask you a generic question.

Let's assume this drug is going to be kept on the list so it can be compounded. At the same time, an IND turns into an NDA, and we have an approved drug product. What's going to happen to the drug that is then still on the to-be-compounded list?

MS. BORMEL: Dr. Venitz, are you asking if a drug is subsequently approved that was on the bulks list?

DR. VENITZ: Correct.

MS. BORMEL: The statute under 503A provides for the use of a bulk substance that is a component of an FDA-approved product. So if something that's on the bulks list is subsequently approved by the agency in a dosage form, then it would be able to be compounded under 503A.

DR. GULUR: I'd like clarification on that to the opposite. If the IND is not approved, if there are safety concerns that are revealed in that process, how would that reflect on the 503A process?

MS. BORMEL: If the bulk substance was on the list?

DR. GULUR: Yes.

MS. BORMEL: Well, I think the agency, depending on what type of safety concerns were available and what happens if it were already on the list, anything that we do is by rulemaking. So if we had concerns, and we found out about them, and let's say there was information that was available publicly, then we might bring it back to

the committee or we may consider another category for the product, because we do have a category 2 for known safety risks for bulk substances that are known to have safety concerns.

DR. GANLEY: Could I clarify something, too? There have been situations where we were aware of some safety issues in an IND. The only situations that we can publicize are if that was already in the public domain.

So the situation that you explained, I don't know. It becomes a legal issue, whether we could divulge the information in an IND, because they're confidential. So if there were safety issues and it wasn't in the public domain, we'd have to get our legal staff to give us some type of authority to make that information available publicly.

So it's not that we would necessarily go out with a proposed rule stating if there's a determination that we can't make that information public, to go back and revisit that list. At least, that's my interpretation.

DR. DOHM: I think that's right. I mean,

obviously, if we had information in our hands that suggested that there was a significant safety concern that wasn't available to us at the time in which we put something on the list, we'd have to find a mechanism to address that safety concern, be it through rulemaking or otherwise.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Robin Bogner. Maybe you can help me. I'm going to ask a question that seems like an obvious one. So if we do not put this on the list, it cannot be compounded with?

MS. BORMEL: That is correct.

DR. BOGNER: So what we are telling patients in the United States is that you can take this supplement on your own without any input, but you cannot get it from a compound pharmacist pursuant to a prescription from somebody who's giving you primary care?

DR. GULUR: I'll let the FDA -- yes. Go ahead.

MS. BORMEL: The thing to keep in mind is that a dietary supplement is basically a food.

It's not intended to treat or mitigate a disease. And when we put a bulk substance on the 503A bulks list, that is intended to be used as a drug.

So there's a difference. There's a legal distinction between when something is available as a dietary supplement, which is a whole different regulatory scheme than when something is placed on the 503A bulks list.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: Could you maybe talk a little bit then about how that affects the way that a dietary supplement can be marketed to patients as opposed to how a compounded drug might be able to be marketed to patients and to providers?

MS. BORMEL: For the dietary supplement question, I'm going to defer to CFSAN.

DR. WELCH: Hi. Cara Welch. Dietary supplements can make a number of claims. They cannot claim to treat, cure, prevent, or mitigate a disease, but they can claim to help the structure or function of the healthy human body.

So they can make general nutrient content

claims, talking about the level of the ingredient. They can make some health claims. It's particularly to reduce the risk of a disease. Those are authorized by FDA. They're reviewed and authorized by FDA, those that meet significant scientific agreement.

Then there are these structure function claims. That's how we loosely refer to them. They're described in Section 403(r)(6) of the Federal Food, Drug, and Cosmetic Act. It's a general health claim or a claim to maintain the structure or function of the healthy human body.

DR. GULUR: Any further questions or clarifications? Dr. Patel?

DR. PATEL: I wanted to go back to the effectiveness studies. I wanted to ask the FDA the question regarding what they look for when drugs that are formally FDA approved for similar indications. Are they typically, in this patient population, looking for trends in improvement?

DR. FURLONG: I don't know if Jean is still here. I'll defer to a psychiatrist.

DR. KIM: What was the question again?

DR. PATEL: The question is, I don't know enough about the patient population, how the studies get carried out. So the question is about the effectiveness studies that are quoted based on which we're going to make a decision to add it to the list or not. And there were some inferences made earlier about how the trials are very similar to the trials that the FDA looked at for drugs that are FDA approved for a similar indication.

So the question is, in the studies evaluating pregnenolone, they noticed trends towards improvement and that a dose to response was not necessarily seen. So is that typically what's seen in the studies when you're evaluating a use of a drug for this set of indications, schizophrenia and bipolar specifically?

DR. KIM: I work in a division where we're focused on the FDA-approved drugs, like not the bulks, but the ones that get prescribed, and the standard of efficacy is much higher. We don't just look at trends. It has to be statistically

significant. And the sample sizes are much larger than in the trials that were cited for the bulks.

DR. GULUR: Thank you. Dr. Jungman?

MS. JUNGMAN: So I think we got to the first part of my question, but not to the second, which I was trying to solve the difference between how you can market and advertise a dietary supplement as compared to a drug, so I appreciated Dr. Welch's explanation about dietary supplements.

It's my understanding that there is more latitude to market or advertise a compounded drug for specific health conditions than there is for a dietary supplement. In my mind, that has always been one of the big distinctions to help me consider why you might want to either put or not put a drug on the bulk substance list that is available as a dietary supplement.

So I was hoping for some clarification on that point, and I think we kind of only got through the first part of that.

MS. BORMEL: I think from the perspective, if something is placed on the bulks list, the one

thing that the statute says is that the information about it can't be false or misleading. So if there is information out there about using this particular bulk for a particular disease or something of that nature, provided it is not false or misleading, you could state that.

DR. GULUR: I think I'd like to just clarify a little bit there, too. So essentially, the difference here being that for dietary supplements, you cannot make the claim to treat, cure, or prevent disease. However, for a compounded substance, you can state that it treats, cures, or prevents disease?

MS. BORMEL: Yes.

DR. DOHM: Not entirely, I think. Cara, you might want to flush this out a little bit more with qualified health claims. But I think the key is that there are going to be some limitations on what you can say about what we call drug claims if you're in a dietary supplement world that will not exist for a drug itself. So there are differences in what you can say depending on how your product

is regulated.

DR. WELCH: I apologize for skimming over these quickly. There are a variety of claims that a dietary supplement can make. To go through them, the three different kinds of claims, the first is a nutrient content claim, which is really just labeling or claiming the amount of a nutrient in your product, high, low, X percent, something along those lines.

The next claim is an authorized health claim or a qualified health claim, and those are available to foods as well as dietary supplements. Authorized health claims are authorized by FDA by regulation -- or by rulemaking, excuse me. And they are reviewed by FDA, and then the limitations around the claim as well as the text of the claim is in the rulemaking. They have to meet significant scientific agreement and are specific to reducing the risk of a disease.

A qualified health claim is similar, except it is qualified because it for some reason or another didn't meet significant scientific

agreement. So it isn't added to the regulation, but it is issued a letter of enforcement discretion from FDA clarifying the information around the claim, why it didn't meet significant scientific agreement, and then the text that is appropriate to use and the type of product you can make it in. Again it should be limited to reducing the risk of a particular disease.

Then the last is that broad claim. We in dietary supplements refer to them as structure function claims, and they're specifically to maintain or effect the structure or function of a healthy human body.

Common ones, it's actually really hard to explain some right now, but we're not talking about a disease, we're not talking about obesity, but we're talking about weight loss or the function of the body.

Some of the specifics that were laid out in our final rule around this, we can talk about memory, aiding memory, but not about Alzheimer's or dementia. So it's that differentiation between the

structure or function of the healthy human body versus when you get into the disease realm.

DR. GULUR: Dr. Mixon?

MR. MIXON: Compounders are prohibited from making specific health claims for their compounded medications, and I'm pretty sure there are warning letters out there for compounders who have done so.

DR. DOHM: That might be under state law. Under federal law, the restrictions on advertising and promotion were initially struck down by the U.S. Supreme Court, and then they were removed from Section 503A when the DQSA was enacted. However, you might be referring to warning letters that might have suggested that claims were false and misleading.

DR. GULUR: Dr. Johnson?

DR. JOHNSON: I would just add that I'm not sure about the warning letters that you're referring to, but we have, during the course of some of these reviews, found older warning letters, before DQSA, that at this time would not have been issued. We would be using enforcement discretion.

I believe that some of the warning letters are not consistent with our current view, and I don't know if that's factoring into some of the thinking that you're explaining.

DR. GULUR: Yes. Dr. Davidson would like to comment.

MS. DAVIDSON: I wanted to follow up on Dr. Bogner's question and get continued clarification from FDA. It's still my understanding that a physician could direct a pharmacist to compound substances that are available as dietary supplements for an individual patient, even if it's not on the bulk substances list.

That's the question. And if that's still true -- I mean, is that your understanding, older members? And if that is the case, then the only concern I would have would be how is a pharmacist to determine the quality of that dietary supplement versus a very specifically C of A pure substance?

MS. BORMEL: Let me see if I can address your question. If a physician wants a compounded

dietary supplement?

MS. DAVIDSON: Or a prescription medication for an individual patient, could the pharmacists go use a dietary supplement, not the pure bulk substance, but a dietary supplement, as the source of the compound? I believe Jane Axelrad told us that that was the case in a previous meeting.

MS. BORMEL: If you're purely compounding something as a dietary supplement --

MS. DAVIDSON: No. It would be a prescription medication.

MS. BORMEL: Then the substance that you're using has to be on the bulks list.

MS. DAVIDSON: That is a significant detour from our previous understanding, and I can pull up our notes.

MS. BORMEL: I don't believe so, but we can look at that. But I remember the discussion several committee meetings ago about what happens if a pharmacy wants to compound a dietary supplement from dietary supplement ingredients. Our jurisdiction is only over the compounding of

drug product under 503A. And under 503A, we have a scheme set out that you have to use bulk substances that are components of FDA-approved products subject to an applicable USP monograph or on the bulks list.

It's talking about making a drug product, but when you use something that is available as a dietary supplement over the counter and you're compounding it to make a drug product, that ingredient has to be on the bulks list or subject to an applicable USP monograph, or has to be a component of an FDA-approved product. I don't think that's ever changed.

MS. DAVIDSON: So for clarification, dietary supplements are dietary supplements, but bulk substances are something else entirely.

MS. BORMEL: When you intend to take a dietary ingredient or dietary supplement and you intend for it to treat, mitigate, cure a disease, it becomes a drug. So if you are, for example, taking pregnenolone, and you intend it for one of the uses that we described, and it were on the

bulks list, for example, you wouldn't be compounding a drug product.

MS. DAVIDSON: So if I had a pediatric patient -- I don't have patients; I'm a pharmacist. But if I had a pediatric patient, as a prescriber, and I needed to use one of these substances, my only option would be to direct the parent of that child to go out and divide up that dosage form, the dietary supplement, the best they could. I could not direct a pharmacist to compound that into a weight-based appropriate dose for that individual patient.

DR. FURLONG: Maybe I can take that. So when we looked at what's available now on the market, in the dietary supplement arena, the doses range from I think 5- to 100-milligram capsules. I think you could probably cover most of your needs with that.

MS. DAVIDSON: For this particular substance, for globally. I think for the new members, I think it's important to have an understanding of what it truly means for access if

we do not allow a substance to go on the list.

I was mistaken clearly for the previous seven meetings thinking that a pharmacist could still go compound with a dietary supplement if directed by a physician to do so because a dietary substance is not a bulk substance, but I clearly misunderstood that.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: I would just mention that the other option there would be to do it under an IND, which we've come back to that again and again at these meetings.

DR. GULUR: A few times. Dr. Bogner?

DR. BOGNER: I'm trying to get this, what we're going to vote on momentarily, when discussion has ceased. In the previous vote we took on L-citrulline, there was a proviso that it only is for oral. Are there any limitations, either treatment for particular diseases or delivery route in this case?

DR. GULUR: In the past, we have been able to limit the delivery route, but indications, I

don't believe, we have done.

Could you clarify that?

DR. DOHM: That's correct.

DR. GULUR: So you can limit to the oral route, but not for indications.

I actually have a question for Dr. Mixon just to clarify on what a compounding pharmacy may state or may not state. You're just randomly looking at pregnenolone through one of the compounding pharmacies, and what it states here is, "Use for fatigue, increased energy, enhancement of memory, as well as decreasing stress and improving immunity, the improvement of libido and sexual energy.

"It is also used for Alzheimer's disease and skin disorders such as psoriasis and scleroderma. Women use pregnenolone for the treatment of endometriosis, symptoms of menopause, and premenstrual syndromes."

So would you consider this to be a typical statement from a compounding pharmacy?

MR. MIXON: I can't state what's typical. I

just know how I was taught, and I was taught not to make specific medical claims for individual compounded preparations, that we could advertise our services, but we could not make specific medical claims. That's the purview of a manufactured drug.

DR. GULUR: Thank you. And for the FDA, is this a statement that, under federal law, is allowed because the substance currently is considered compound?

MS. BORMEL: Can you repeat the statement, please?

DR. GULUR: "Pregnenolone is used for fatigue, increased energy, enhancement of memory, as well as decreasing stress and improving immunity, and improvement of libido and sexual energy. It is also used for Alzheimer's disease and skin disorders such as psoriasis and scleroderma. Women use pregnenolone for the treatment of endometriosis, symptoms of menopause, such as hot flashes and mood swings, and premenstrual syndromes." It further goes on to say

that the capsules are compounded under the stringent USP 795 guidelines.

DR. DOHM: So many of those statements, I think, would fall in the realm of what we consider to be structure/function claims that are often attached to dietary supplements, and some of those claims are what we would call disease claims, that can be made when they're associated with drugs.

So it's a very nuanced analysis for each of those claims, and they'd have to be analyzed individually to determine whether or not they would be appropriate for a dietary supplement, drug, or both.

DR. GULUR: So Alzheimer's disease as an example would be a disease?

DR. DOHM: Disease, disease claim.

DR. GULUR: Is that something they can make a claim to?

DR. DOHM: A dietary supplement?

DR. GULUR: No.

DR. DOHM: No.

DR. GULUR: This is a compounding pharmacy.

DR. DOHM: So if a compounding pharmacy wants to have a claim associated with the drug that is for a disease, then it would be able to do so as long as it's a drug, and it can't be of course false or misleading.

DR. GULUR: So what is the burden of evidence for this? For instance, right now, we're being asked to review these studies and see what is the evidence for efficacy. What is the burden of evidence on a compounding pharmacy as far as these claims are concerned for disease cures? Dr. Mixon?

DR. DOHM: As I said, they can't make statements that are false and misleading, so that would be one of the federal standards. And then as for whether or not something is misleading, you often look at the body of evidence associated with the statement.

So for example, if the entity said that a particular drug was effective in treating Alzheimer's disease, the question would become what would people understand that to mean. And would they understand that to mean that it's been shown

to be effective, and what level of evidence have they used or relied on to demonstrate that effectiveness?

So it really is a question of expertise and analysis of the evidence, and it's not a straightforward -- I can't give you a really straightforward answer.

DR. GULUR: Dr. Mixon, would you like to comment?

MR. MIXON: I just want to add that what you just read sounds like it's straight out of something you would find in the Natural Medicines Comprehensive Database. So for this substance, which is a dietary substance, I don't have access to it, but perhaps later we can find the monograph on this substance in the Natural Medicines Comprehensive Database and see what it says.

But that's exactly the kind of information you would find in the Natural Medicines Comprehensive Database.

DR. HARROUK: I have a comment here. We did include the NCMD summary in the review. It's in

the background information for pregnenolone. So we did reference the NCMD and what they said.

MR. MIXON: I thought you had, yes. Can you find it?

DR. HARROUK: It's on page 11 of the review. Did you want me to read it?

DR. GULUR: Does it state Alzheimer's disease?

DR. HARROUK: It says, "The NCMD notes that since pregnenolone is converted to estrogen," it says, "The NCMD monograph states that pregnenolone is contraindicated in people with hormone-independent prostate cancer and individuals with seizure." It does not specifically mention Alzheimer's. It says it can cause steroid-related adverse events, including insomnia, nausea, irritability, et cetera.

Correction. NCMD does list Alzheimer's. I just was corrected. I stand corrected.

DR. GULUR: Just to clarify for future -- and we do need to wrap this up, so we'll move on -- it would be very helpful for us,

especially with our newer members, if this could be clarified again, on what can and cannot be included; and when we approve a drug for placement on this list, what are the full implications of that in terms of practice. I know we've been through that before, but it would be worth going through it again.

Dr. Mixon.

MR. MIXON: Real briefly, I just want to mention that FDA has a guidance that says that dietary substances are not appropriate for the use of a bulk drug substance for pharmacy compounding because they're a dietary substance. They're not drugs.

MS. DAVIDSON: Just to clarify, that's a monograph. A dietary substance monograph is not an applicable monograph.

MR. MIXON: Thank you, Gigi.

Committee Discussion and Vote

DR. GULUR: Thank you very much, everyone. With that, we will now end our discussions and start the vote. To read the question, FDA is

proposing that pregnenolone not be included on the 503A bulks list. Should pregnenolone 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.

If there is no further discussion, we will now begin the voting process. Please press the button firmly on your microphone that corresponds to your vote. You have approximately 15 seconds to vote. After you have made your selection, the light will continue to flash. If you aren't sure of your vote, please press the corresponding button again.

(Voting.)

Dr. CHEE: Question 2 on pregnenolone, we have 6 yeses, 5 nos, and 1 abstain.

DR. GULUR: Thank you, everyone. We will

start with the comments. Dr. Carome, if you could get started.

DR. CAROME: Mike Carome. I voted no because the safety profile of this drug has not been sufficiently established, particularly for long-term use. And all the diseases for which it was nominated are chronic diseases, so long-term use would be expected. There's really been no evidence of effectiveness for the nominated uses. So for those reasons, I don't think it should be on the list.

DR. HOAG: This was a very difficult decision and could have gone either way. When you look at products sold as DSHEA, dietary supplements, some of those would have better quality than compounded and some less quality depending on the manufacturer.

Then the compounded products, some of those, will have good quality, some may not, depending on the skill of the compounder. These things are very hard to evaluate. But again, it's a very difficult decision, so I selected yes.

MS. JUNGMAN: Elizabeth Jungman. I voted no. I always struggle with these decisions about substances -- compounds that are available as dietary supplements. It feels a little futile to vote against putting something on the bulk substances list if it can be obtained off the shelf.

While I am concerned about the broader marketing claims that could be made about compounded drugs, I generally agree that it would be better to see patients getting substances from pharmacists and physicians than off the shelf.

I just want to second Dr. Gulur's suggestion that it would be helpful perhaps at some future meeting to get more guidance from FDA about the distinctions between dietary supplements and compounded drugs to help the committee assess why it matters whether something is on the bulks list if it's available as a dietary supplement.

Ultimately, though, if I focus on the four factors that we have all agreed are the ones we're supposed to be voting on, considering the lack of

long-term safety data and potentially severe adverse events weighed against the lack of persuasive evidence of effectiveness and availability of proved alternatives, that led me to vote no.

DR. BOGNER: Robin Bogner. I voted yes because this is available to folks without the benefit of follow-up. And I also note that it's for treatment of conditions that are very difficult for some patients to find full relief.

There was some efficacy in some patients. This is exactly where I think compounding focuses, on the treatment of individual patients. And for that reason, I voted yes not to limit access to patients for this material.

DR. PATEL: As with what all the other members stated, this was a tough decision. However, I did vote no primarily because of three reasons. One is inconclusive evidence of benefit or outcomes, especially comparative to standard of care.

I also have worries about the unintended

consequences of a product that has effects on multiple systems in the body and the worry for how patients would be managed if indeed they had either an adverse outcome or other unintended consequences.

MR. HUMPHREY: William Humphrey. I voted yes. I too struggled with this. I really struggled with either this is a drug or it isn't, regardless of whether it's a dietary supplement or not. And I would a whole lot rather a pharmacist be dispensing this on a prescription of a physician.

Your speaker stated that if a physician felt this was necessary, they could still prescribe it as a dietary supplement. I would rather that come from a pharmacist.

DR. GULUR: Dr. Wall, if you could state your opinion.

DR. WALL: This is Dr. Wall. I voted yes. I think that this is too dangerous of a substance to really be an over-the-counter dietary supplement. I think it's got the perfect place,

having a pharmacist who is personally involved with that patient, so you have a legitimate patient-pharmacist relationship to monitor for all the long-term side effects that can be seen through drugs like this. That's it.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: I voted yes. In my mind, the safety signal was somewhat absent for the treated populations, as evidenced by the lack of increased elevations of downstream hormones in patients with schizophrenia and depression.

It does seem like it may have some promise as an adjunct for treatment of schizophrenia. And if it is held within the triad, where prescribers can carefully monitor for adverse events downstream of treatment, then I feel like that is a better place for this therapy than to have patients going and buying dietary supplements off the shelf, which, as was mentioned, range in strength, a very, very, very huge range of strengths. They may get the wrong one.

Finally, even though there is an IND, it

seems to be a largely non-patentable substance, so I don't believe there is any incentive for some sort of sponsor to do the research development and clinical trials that we require to get this drug approved down the road.

So I voted yes to allow it to be accessible to patients that still need it, in a safer way.

DR. GULUR: Padma Gulur. I voted no for reasons that have already been stated by some. One was the long-term use safety signals for this. I would have to agree completely this is challenging because having a pharmacist dispense this is definitely safer than dietary supplements being used for medicinal or drug-related purposes.

However, there is an IND in process. I won't venture on how much people will be willing to invest in it, but some of what influenced my decision was also questions on the oral availability of this and whether having more complex mechanisms of delivery, which there would be an investment for, I would think in the future. Therefore, there was potential that this drug could

be studied more carefully, long-term safety evaluated and hence, voted no.

Dr. Venitz on the phone?

DR. VENITZ: This is Jurgen Venitz. I voted yes. Like everyone else, this was one of the more difficult votes that I have to make as part of the committee. I acknowledge the limitations of the pre-clinical/clinical safety efficacy information.

I did go through all four criteria, and if it had been just for the first three, I would have voted no. I think what kicked me over to the other side was the fact that the current treatment for the psychiatric diseases is unsatisfactory, and there is at least a signal of promise. And that along with the fact that it's not going to be available under the control of a pharmacy-patient relationship rather than over the counter, kicked me over to the yes vote.

DR. VAIDA: Alan Vaida. I voted no. Although there's been a lot of discussion on this, I did go along with the no long-term safety data, but also that the submission was changed to oral

for schizophrenia and bipolar, yet there was about close to 100 public letters. And when I read through those letters, the majority of those that mentioned this drug were for hormonal replacement therapy and oftentimes as a cream.

So I just have a lot of concern on any control that you could have over this.

DR. GULUR: On the phone, Dr. Fiedorowicz?

DR. FIEDOROWICZ: Yes. I voted to abstain. I didn't feel that the evidence for effectiveness was established for psychiatric disorders, although there were some hypothesis-generating exploratory findings that might encourage further study.

After reading the four criteria and even after the discussion, I was still not clear on how best to balance the four criteria, so I defer to abstain to defer to the more experienced members of the PCAC.

DR. GULUR: Thank you.

With that, we are running a little bit behind time, however, we will move on to the next segment. We will now proceed with Dr. Johnson's

FDA presentation on DHEA.

DR. JOHNSON: So thank you for that interesting discussion with lots of various factors, and we appreciate the complexity of your considerations and the various aspects that you've delved into.

DR. GULUR: Dr. Johnson, I would just ask for a minute of your patience.

Dr. Desai, if you would, introduce yourself since you will be participating in this discussion.

DR. DESAI: Thank you very much, Dr. Gulur. Seemal Desai. I'm a dermatologist in clinical practice in Dallas. I'm also on the board of directors at the American Academy of Dermatology and happy to be a part of the meeting. Thank you.

DR. GULUR: Thank you, Dr. Johnson.

FDA Presentation - Susan Johnson

DR. JOHNSON: Good afternoon. My name is Susan Johnson, and I'm from the Office of Drug Evaluation IV in CDER's Office of New Drugs. And I would just say by way of transition that while this substance, 7-keto DHEA, is related to steroids,

without being flippant, it doesn't even appear on the diagram that we've given you. So it doesn't sit as prominently in steroidogenesis as the other things we've talked about.

I think I just mentioned that as a way of sort of clearing the deck so you can think specifically about this substance and not necessarily align it completely with all the other discussions we've had.

I'd like to thank members of the review team, especially Dr. Zhang and Dr. Hankla, who worked with us in OND on each of the nominated substances, and we appreciate their contribution on all of them.

7-keto-DHEA has been nominated for inclusion on the 503A list and has been proposed for use in weight loss and to treat Raynaud's phenomena. The proposed routes of administration include oral, sublingual, and topical.

7-keto-DHEA, which is also referred to in chemistry parlance as 7-oxo DHEA, is a small endogenous steroid molecule. It's a well-

characterized substance that's nearly insoluble in water, not soluble. While we found no stability data for 7-keto-DHEA, its structure suggests that it is likely to be stable in the proposed dosage forms under ordinary storage conditions.

7-keto-DHEA is synthesized from DHEA, and DHEA was on the steroidogenesis diagram that you saw, and the process may introduce toxic impurities. As we've noted, compounders should use the information on the CoA to identify any potential safety or quality issues.

In conclusion, 7-keto-DHEA is well characterized and likely to be stable under ordinary storage conditions for oral, sublingual, and topical formulations.

DHEA is a precursor for testosterone and estrogen. DHEA is also converted to 7-alpha-hydroxy-DHEA, or 7-beta-hydroxy-DHEA, which are in turn converted to 7-keto-DHEA. There's variation in the literature about whether 7-keto-DHEA can be converted back to DHEA through the hydroxy steroids. If the process is reversible and 7-keto-

DHEA can be converted back to DHEA, then there's potential, as we've just talked about, for downstream effects on testosterone and estrogen levels. We conclude, based on the data that we found, that it's not possible to definitively say whether the reactions are reversible.

We found that 7-keto-DHEA's role in the body is not well defined. We have in vitro data suggesting that it may induce estrogen-mediated gene expression and may help regulate conversion of inactive to active cortisol. Despite lack of demonstrated androgenic activity in vitro, the World Anti-Doping Agency, which is a foundation established in 1999 by the International Olympic Committee, has banned 7-keto-DHEA as an anabolic steroid.

We found a single study of the endogenous levels of 7-keto-DHEA in 8 women which varied during the approximately 16-hour study period. Topical administration of a total daily dose of 25 milligrams 7-keto-DHEA in healthy males for 5 days, or 8 days with measurement out to 100 days

following treatment, appeared in two different studies to show effects on levels of testosterone, estradiol, and other endogenous substances.

We found little non-clinical safety data for 7-keto-DHEA, but did find one repeat dose toxicity study. The treatments dosed by oral gavage are listed on the slide, and the maximum dose of 140 milligrams per kilogram was defined as the no-observed adverse effect level in Rhesus monkeys.

Although the acetate ester is not the subject of the nomination or the review, we looked at related non-clinical safety data. We found information supporting a NOAEL of 500 milligrams per kilogram in Rhesus monkeys dosed orally and a negative AMES test. The specific correlation of data from the acetate ester to 7-keto-DHEA is not known.

In the FAERS database, there was one case in which a male patient reported a fivefold increase in testosterone levels. The 14 CAERS reports with which 7-keto-DHEA use was reported were confounded by the use of multiple supplements. We found no

clinical trials or published case reports for 7-keto-DHEA.

In conclusion, we found little safety data specific to 7-keto-DHEA. We have not identified safety concerns, but we cannot rule out their potential, particularly with long-term uses we've discussed.

Primary Raynaud's phenomenon is idiopathic and evidences episodic vasospasm of the arteries and arterials in the extremities and most often manifests as pain and pallor followed by cyanosis in the fingers, toes, and ears. Secondary Raynaud's can be attributed to a number of disorders that affect the vasculature.

The proposed use of 7-keto-DHEA in the treatment of Raynaud's phenomenon is not supported by clinical trial data. There is a 2003 publication by Ihler, et al. in which the theoretical benefit of 7-keto-DHEA is suggested based on the potential for 7-keto-DHEA to induce metabolic thermogenesis. This publication does not describe a clinical trial or efficacy data. We did

find one case report of an individual who was reported to have improvement in association with 7-keto-DHEA dosing of their Raynaud's syndrome.

Thermogenesis has also been postulated as a potential mechanism for 7-keto-DHEA to have an effect on the treatment of obesity. We did find observational data of 7-oxo, or DHEA as it was called in that study, in obese children, but we found no interventional clinical trials.

Based on the published literature, 7-keto-DHEA has at least a seven-year history of being used in pharmacy compounding, although we were unable to establish the extent of its use. 7-keto-DHEA is available as a dietary ingredient in dietary supplement products.

In conclusion, 7-keto-DHEA is well characterized and likely to be stable under ordinary storage conditions for oral, sublingual, and topical formulations. We found little safety data specific to 7-keto-DHEA. There is literature about 3-acetyl 7-keto-DHEA to a limited extent. We have not identified safety concerns, but cannot

rule out their potential, particularly with long-term use. We found no clinical evidence of effectiveness for 7-keto-DHEA in Raynaud's phenomenon or weight loss.

7-keto-DHEA has been used in compounding for at least 7 years and is available in dietary supplement products. Overall, a balancing of the four criteria in FDA's opinion weighs against 7-keto-DHEA being added to the list of bulk drug substances under 503A. I'm happy to take questions.

Clarifying Questions from the Committee

DR. GULUR: Do we have any clarifying questions? Dr. Carome?

DR. CAROME: Mike Carome. In the FAERS database, there was the one case where a male patient had a fivefold increase in testosterone taking this product?

DR. JOHNSON: Correct.

DR. CAROME: Is it plausible that that increase in testosterone could have occurred because of exposure to this drug?

DR. JOHNSON: I don't think we can assess the relationship based on the information that was there. As an editorial component, I didn't choose to put in the report to begin with. The reason this gentleman reported this and there were no clinical measurements associated with it, but he had been told that the substance would not affect his testosterone levels and in fact it did. And that was one of the reasons why he chose to report. But that's anecdotal, and that's all the information we have. We have no clinical information.

DR. CAROME: Just to follow up, maybe more generically than just this case, for the World Anti-Doping Agency, it's classified as an anabolic agent. Given its structure and where it falls, is it plausible that it could indeed possibly increase testosterone or related hormones?

DR. JOHNSON: I think, to be as scientific as I can be about this, the literature seems very mixed about whether or not 7-keto-DHEA can be reconverted to DHEA. I think that the predominant belief is that it cannot be, and I don't know what

mechanism of action those effects would have if it were just a downstream metabolite of DHEA.

But to be scientifically accurate as well as I can, I don't think we know the answers to any of this. The literature is very mixed.

DR. GULUR: Dr. Desai?

DR. DESAI: Seemal Desai. Thank you for your presentation. As a dermatologist who treats skin disease, I was interested to see Raynaud's phenomenon listed because that's one of the most difficult things we treat in patients with connective tissue disease. However, I was concerned that there was only 1 case report, as you mentioned.

Did they possibly postulate the mechanism of action behind how this worked in that, just considering that it's more of a vascular disease manifestation?

DR. JOHNSON: So as I understand it, the idea that 7-keto-DHEA could be associated with thermogenesis, which as I understand the literature, metabolic thermos genesis is mostly

theoretical mechanism, but the oxidation of fatty acids in the mitochondria might in fact create a scenario to essentially warm, and that's the link. It's plausible. It hasn't, in our estimation, been demonstrated.

DR. GULUR: Any clarifying questions from our members on the phone?

(No response.)

DR. GULUR: Thank you, Dr. Johnson.

DR. JOHNSON: Thank you.

DR. GULUR: We will now proceed with the nominator presentations. We have one presentation, Mr. Tom Wynn from Fagron.

Nominator Presentation – Tom Wynn

MR. WYNN: Thank you for allowing me to come and speak to you today. My name is Tom Wynn. I'm a pharmacist. I've been a pharmacist since 1994, and I currently am employed with Fagron, and we do actually sell 7-keto-DHEA.

7-keto-DHEA is a metabolite of DHEA, and I think the FDA did also speak to that. When administered to humans, 7-keto-DHEA can also be

metabolized into its hydroxyl, in the epimers, and the FDA talked about that as well. I think the characterization is something that's not really being argued here, that it's definitely very easily characterized as a hormone, or a hormone metabolite, I should say.

The information that I found, I know that they were talking about can DHEA go back and forth from 7-hydroxy-DHEA to DHEA. The information I was finding was showing actually an irreversible reaction, and it involves the enzyme, 11-beta-hydroxy steroid dehydrogenase, which then breaks down to DHEA and takes it to the 7-alpha-hydroxy-DHEA, which then can reversibly flux into 7-keto-DHEA, and like we mentioned, the other epimers of that particular metabolite.

This has been up several times, and I do love this particular diagram. I think it's something great to have in your pharmacy because it answers a lot of questions sometimes when you're dealing with patients.

What I note is on there is that DHEA is on

there in the little corner and all the different things that DHEA can be turned into. And if indeed we do have that irreversible reaction, we know that we're not going to have the threat of maybe producing estradiol, or cortisol, or other metabolic or other hormones in the body that could cause other adverse effects with what we're trying to treat.

I like to think of this as the symphony of the body, and we definitely want to keep that intact while we're trying to help patients when we're treating different symptoms or disorders.

In human therapy, there are some undesired responses to administer DHEA because it does elevate testosterone and dihydrotestosterone concentrations in women, and that has been documented.

The 7-oxo steroids should prove to be more useful therapeutic agents than DHEA, and they have shown to be a little bit more active. They're not rheumatized and cannot be converted into testosterone. And that was a study that I found

listed there at the bottom that is saying that you're not going to have it convert back to testosterone, which means it's probably not going to go through that DHEA pathway as well.

Now, as far as safety goes with 7-keto-DHEA, looking through I did find that they did do a safety assessment of a mammalian microsome reverse mutation study. They were looking at the 3-acetyl 7-oxo-DHEA and its metabolites. This is a very common study that they do when they're trying to determine different types of mutagenicity, and they'll use bacterial strains to do that. In the results, they concluded that it was safe and well tolerated and normal healthy men at doses up to 200 milligrams a day for 4 weeks.

Also here, this is actually the same study, and I just kind of wanted to get into it a little bit more in that when they looked at it, there was no differences in clinical laboratory values when they monitored adverse experiences between treatments in placebo groups. In general, blood hormone concentrations were not affected by the

treatment of the 7-oxo-DHEA.

So even there, they were looking at other hormone levels and not really finding significant changes in hormone levels, although they're not specified specifically in this abstract which ones they're looking at, but they're not seeing changes. More likely, they're looking at testosterone, estrogen, and the other hormones that are in that cascade that we mentioned before.

So what we're seeing again is that it's normally well tolerated in normal doses. And in this case, they determined that normal dose to be 200 milligrams a day for 4 weeks for this particular study.

Here, when we're looking at just 7-keto-DHEA, it would be considered an ergosteroid or biologically active metabolite, synthetic derivatives of DHEA. Within a single experiment over the range of 0.01 to 0.1 percent of the diet, they found that it was actually 2.5 times more active than DHEA. And I think they're looking at more not so much active in its ability as a

hormone, let's say the hormone aspects of DHEA, but again, looking into how well it actually helps with thermogenesis, which is something that the DHEA rep brought up in their talk.

DHEA itself can help with thermogenesis, but you have to use a lot more of it to have that happen. The studies that I saw, they were using huge amounts of DHEA, whether it be 1600 milligrams or huge amounts in comparison to what you would normally do in animal studies to kind of show that they were getting some type of thermogenesis. But when you're talking about 7-oxo-DHEA, the metabolite, it is a bit stronger doing that. The doses can be much smaller, so you can get the results that you want.

Again, what is thermogenesis? It is, again, the idea that what's going to happen is that you can, again, cause that mitochondrial breakdown of essential fats and increases the temperature. And I'm not talking about going up to 100 degrees. These are small increases in temperature. The body's normal response then is to open vascular

areas to the extremities, so the hands, the feet, and that's going to allow that heat to dissipate.

What you have in some of these patients that are suffering from different afflictions, that's important because you want to increase that circulation. And we can do that using the body's own natural response to an increase in temperature.

This particular one here, again, they were just looking at activity of different steroid glucuronides, 7-oxo derivative, again talking about it being more active in the parent steroid DHEA and devoid of adverse effects in rats, monkeys, and humans in this particular study.

Now, something else I will stop for a minute and mention about safety, too, is, we've got to remember that this is something that's produced in the body. It is a normal metabolite of DHEA. It's an excretionary form. We will excrete it in the urine to get rid of that particular -- maybe to break down DHEA and to get rid of its levels.

So because of that, it's relatively thought of as safe in my mind because it's something that's

produced in a normal metabolic functioning, not something that's in error like a cancer or something.

I like to refer to it the same as looking around, I see that most of the members have water in front of them, except for one. Charles there decided to go with Ocean Spray. He was a different guy, but that's okay. But everybody has water in front of them, and water is in general thought of to be safe.

Now, it's something unlike 7-keto-DHEA that's quite a metabolic process. We do take it in. We need it every day. But water is relatively safe unless I would jump in the ocean and try to swallow all the water in the ocean. Therefore, it becomes toxic.

So I think it's not so much we're worried about the safety of 7-keto-DHEA, but we're worried about at what limit is that safety. It's a metabolic process in the body that creates it. It should be generally safe because it's already there. What we need to determine is what's the

limit. How much becomes unsafe?

This one, I also wanted to mention. It was brought up several times that it is available over the counter, many dietary supplements since 1997. So even though we have had many discussions -- I won't get into it about how they determined safety profiles -- I think that it's out there and available. That says something to that as well.

So efficacy, again, this particular study was talking about the effects again of the mitochondrial membrane potential, and they found that feeding 7-oxo-DHEA decreased body weight gain in rats.

Again, the whole idea is thermogenesis, again, if we can start to create changes in how we metabolize fats, then we of course can then change our weight profiles. And that's kind of where they're going with this. This one was done in rats, not in humans, but they did find that they did see some weight changes in those animals.

Now, as far as Raynaud's phenomenon goes, it was mentioned that it's something you wanted to

hear more about. This particular study was already mentioned, and they did talk about that they were able to have very helpful prevention of Raynaud's attacks. I actually have personal experience in this. I'd like to share a couple of those with you.

As a pharmacist, I did have an instance where a cardiologist had a patient who had Marfan's syndrome. Marfan's syndrome is a connective tissue type, and I won't really get into all the aspects of that. But it's a connective tissue disorder. And Raynaud's is often associated with Marfan's.

This particular one was a 12-year-old child who was having Raynaud's symptoms along with Marfan's. They do tend to have congenital heart problems. So the normal things you might think of to do is why don't we use something like a commercially available calcium channel blocker, or some type of vasodilator that they can take, that then, again, would do the same thing. It's going to open and vasodilate the periphery, again, so that we increase blood flow and we can get that

sensation away, the cold sensation and the different sensations they had with Raynaud's.

But we didn't want to do that because this patient again had some different heart abnormalities associated with the Marfan's. So we decided to go ahead and try the 7-keto-DHEA. It was the physician's decision to go ahead and start at 10 milligrams and then kind of work up until we got the response that we wanted.

It turned out that, actually, at 12 years old, 10 milligrams worked out just fine. Patient took the 10 milligrams. The symptoms were resolved. They were doing fine, but as they aged, they did have to increase the dose. And by the time he was 18, he was taking 30 milligrams a day. Those doses are much lower than the doses that we saw before, where they were doing 200 milligrams.

That's what I'm getting at, is we don't need an ocean of this particular 7-keto-DHEA to get an effect. What we need to do is we need to work together with physicians, pharmacists, and patients, and maintain that connection so that we

can work together to figure out what proper dose is going to take care of that.

Now, along with that, questions might come up, well, how do you know that you actually delivered 10 milligrams? My pharmacy and what we recommend as a group, as a supplier, to the pharmacies that we deal with, you need to have some type of potency program where you're actually checking the particular items that you compound, and we did.

We checked 7-keto-DHEA to be sure that it contained the 10 milligrams that we said that we did in our processing. We also had different quality checks there to be sure that who was compounding, that they did it the same way and that we could consistently create that again the way that we wanted.

Another way that it came up was not necessarily for Raynaud's. It was, but this was a little bit different, too. I had an endocrinologist contact me and had a patient who actually was having -- they figured out it was not

making enough 11 beta-hydroxy-steroid dehydrogenase. That particular enzyme not only helps with the conversion of DHEA to 7-keto-DHEA, but also cortisone to cortisol.

This patient was more fatigued, was having some problems and issues with Raynaud-type symptoms and their extremities, and wasn't responding well to some of the other treatments. When he finally figured out that was the issue, he wanted to put this patient on 7-keto-DHEA, which we did.

This particular patient was an adult, so we did start off at 30 milligrams, figuring the other adult, why don't we start there, and that worked out find for them, too. They were not having a lot of other hormone issues.

Why that's important is because this patient was also on hormone therapy, and the hormone therapy wasn't working out right because they weren't having the same conversions they should have. They weren't breaking down cortisone and cortisol, so the results were varying when they tried to do other types of hormone therapies.

Now, treating it with the 7-keto-DHEA did not affect that negatively or positively. It simply was able to take care of the symptoms that they wanted, which were the Raynaud-type symptoms that they had.

So those were two instances in practice where I was able to help out patients. And, again, when you're talking about Raynaud's, you may be talking a subset of the population, maybe 200,000 people.

Well, I take that back. When you talk about Marfan's, that's only about 200,000 patients, and most of them can have a different type of Raynaud-type symptoms. Raynaud's is actually more like 10 to 15 million. There are quite a few patients out there that are affected by Raynaud's.

My question is, of those patients, how many of them are going to have some type of cardiac abnormality possibly where the usual course of action will not be available to them? We have an option here, 7-keto-DHEA, which can help Raynaud's. Even though the information may not be several

placebo-controlled studies, we do have some information here that helps us to give this as an option for those patients.

So in conclusion, I do feel and it is definitely well characterized by HPLC, safety has been shown in animals, and there was some indication of human studies. Safety was met, no resistance for the dietary supplement status, so it's been out for quite a while.

So at some point, it would have had to have been at least looked at the processing to be sure that it can be stable in that process and that it has been shown effective.

Now, weight loss was one that I never had experience in, but definitely Raynaud's, I think there is a definite need there, and it definitely can be quite useful for those physicians wanting to treat Raynaud's syndrome. And again, I think the key is to remember, in compounding, we're dealing with an individual patient. We're not trying to deal with the entire public. So when physicians call, we have this available to us as an option.

I think it's important to make sure that that's there so that there's not patients out there that are maybe suffering from an ailment that can't be treated just because we don't have an option available.

You might say, well, they could have used the over-the-counter DHEA. Could be true, but, again, dosing can vary there, because although I think there are much higher strengths than 7-keto-DHEA, and maybe at even 30 milligrams available over the counter, I don't know that you need much more than that.

But what if there was a suspension that had to be made? I mean, these types of Marfan's syndromes start out at birth, so these kind of symptoms can go on in kids.

How would you make a suspension out of the over-the-counter 7-keto-DHEA when you're not allowed to create any compound from it? You're forcing these kids to try to swallow capsules, parents trying to open them up, and again, dosing might be a little bit more difficult.

Clarifying Questions from the Committee

DR. GULUR: Thank you. Do we have any clarifying questions? Dr. Carome?

DR. CAROME: Regarding your conclusion that it has been shown to be effective in weight loss and Raynaud's, are you aware of any randomized placebo-controlled trials that support that claim?

MR. WYNN: I'm afraid I don't have any randomized placebo-controlled trials. I can only go from my own personal clinical experience and knowing that, again, there wasn't a lot of research out there that was put. There was that one article that drove us to go ahead and try it ourselves.

I had two patients. I had two successes. I know that's a very small size, anyway, but I feel that definitely with the literature out there showing that 7-keto-DHEA does -- there were articles I presented that show that it does help with thermogenesis. I think that is definitely a plausible, even as the FDA mentioned, effective way to treat that.

When there's no other option available, like

when you can't use nifedipine or some of the other commercially available because of the side effects, there has been and has been brought up that, for instance -- and this is not quite as similar -- in anti-fungal preparations, the topical products were approved when they only had a 30 to 40 percent effective rate because there was nothing else available.

So if you're saying that I'm not going to approve this because I don't see the studies on effectiveness, but I do see some effectiveness, there are drugs that have been approved already that have very low effectiveness rates because there's a need. And I think there is a need because of the amount of patients that are out there. That 10 to 15 million that have Raynaud's, a lot of those could benefit from having this available to be compounded.

DR. GULUR: Dr. Jungman?

MS. JUNGMAN: This may not be a fair question to ask you, but I'm going to throw it out there anyway, what your sense is of the overall

market. So compounding of the substance, is it typically for Raynaud's or is it more often for weight loss or even for hormone replacement therapy?

MR. WYNN: Sure. Personally, I never saw it for weight loss. It was only for Raynaud's, and that's what intrigued me the most, because I knew there was a patient population. People would come in and talk to you. As a pharmacist, people come in. They tell you about their different ailments, what they're doing, and what's not working.

So I saw more of a benefit for that than over the weight loss myself, so I can't really contest the weight loss because I never really worked with a patient and a physician to treat somebody for that, but I do feel that the Raynaud's could be huge just by looking at the sheer number of them that are out there and looking at what's currently available.

We're not really focusing on -- we're taking the effects of other medications that are approved and we're using it, but they tend to have side

effects. And this has a much lower side effect profile. And as we went through, we could not find any necessary side effects. I never saw any myself. Most of the studies brought up that side effects are very limited.

So I think it's a better option for a lot of the patients, especially the ones who might have some type of congenital heart defect along with the Raynaud's.

DR. GULUR: Dr. Desai?

DR. DESAI: You mentioned a study of safety with the 200-milligram dosing that I believe was for four weeks. Do you know the duration of that, how long they track that out, or was it only for that 4-week interval?

MR. WYNN: The four weeks is all that I know. I know, from personal experience, the patients that were on it -- like I said, the one child was on it from 12 to 18 before I stopped seeing them again. So they were on it for years, a much lower dose, of course. Again, they were only on 10 milligrams up to 30 at the end.

But again, I think that's where it's important to have that relationship with the physician, and the pharmacist, and the patient so that when you want to try to help them in a particular situation that's a niche situation like this -- we see in the dose 200, we knew let's not go there. Let's start at a lower dose, and we can work up, see how you're doing, if it's working great, because the idea is to find the lowest effective dose for that particular symptom.

DR. DESAI: What is the most common formulation you're getting prescriptions on this for?

MR. WYNN: Most commonly, it was capsules because actually the kids -- he was 12. He could swallow, and the other was an adult. So I didn't really see a lot of suspensions, but I know it could be out there. And after our talk of not being able to use the nutraceutical over the counter, I think there could be a need for that if word kind of gets out.

It was more or less me. I wasn't promoting

this. It's was more or less physicians who knew of me, knew what I could do. When they had a problem like this, they contacted me and asked me about it.

DR. DESAI: Thank you.

DR. GULUR: Dr. Johnson?

DR. JOHNSON: I'd just like to make a couple clarifications. The clinical study of 200 milligrams per day for 4 weeks in normal healthy men was not conducted with 7-keto-DHEA. It was conducted with the acetyl ester, 3-acetyl 7-keto-DHEA.

It's perfectly possible for that substance to have been nominated for the 503A list. That is not the nominated substance. And we knew that in the marketplace, there are products called 7-keto that actually contain the acetyl ester.

So we did do some digging around to see if we could find information that related the two in terms of efficacy or safety, and we didn't find any. They may be related pharmacokinetically. The acetyl ester may be converted to some extent to 7-keto in the body, but that was the limit of the

ability to make translation. So we do not have a clinical study of 7-keto-DHEA.

The other observation that I would make is that the paper by Ihler in 2003 was a case report. It was not a clinical study. Ihler went ahead and recommended that the thermogenic construct may be helpful in prevention of primary Raynaud's attacks by increasing metabolic rate and inhibiting vasospasm, but it was purely theoretical.

DR. GULUR: Dr. Ganley?

DR. GANLEY: I just wanted to make one point. In your slide, you mentioned that its safety met no resistance from the FDA for dietary supplement status. That is generally not reviewed by FDA. The burden is on the FDA to prove that it's not safe or establish that it's not safe, so that's not even a factor in getting on the dietary supplement market.

MR. WYNN: It doesn't have to be safe to be over the counter?

DR. GANLEY: There's no review of safety to get over-the-counter dietary supplement status.

The burden on FDA is quite high to establish something is not safe as a dietary supplement.

MR. WYNN: This one's been out for how many years?

DR. GANLEY: Yes, I understand. But we're going to come to some later things where there are several hundred reports of adverse events, for example, when there is resveratrol. But people are on generally more than 50 ingredients in their dietary supplements, and there's a lot of serious adverse events. It's hard to understand whether these are related or it's related to disease or what.

So even in situations in the past where there have been serious adverse events such as liver toxicity, it's been very difficult for FDA to take action in those cases.

DR. GULUR: Any further questions from our members on the phone?

(No response.)

Committee Discussion and Vote

DR. GULUR: Thank you very much.

We do not have any open public hearing speakers. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

We will now begin the panel discussion. Any comments from the group? Dr. Carome?

DR. CAROME: Mike Carome. So I'll just note that the sole evidence for Raynaud's was a couple of reported cases of a patient improving, and such anecdotes really fall far short of the type of evidence I think one would want to even begin to assess effectiveness.

We're not hearing reports of the cases in which patients got an intended response, so obviously it's a biased status sample. And those that do respond, it could be simply placebo effect. And without randomized placebo-controlled trials, we have no basis to judge where the product is effective for that use.

DR. GULUR: Thank you, Dr. Carome.

Any further comments during the discussion period?

(No response.)

DR. GULUR: We will now end our discussions and start the vote. If you vote no to this question, which is, FDA is proposing that 7-keto-DHEA not be included on the 503A bulks list. Should 7-keto-DHEA 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 component of an FDA-approved drug.

If there is no further discussion, we will now begin the voting process. Please press the button firmly on your microphone that corresponds to your vote. You will have approximately 15 seconds to vote. After you have made your selection, the light will continue to flash. If you are unsure of your vote, please press the corresponding button again.

(Voting.)

DR. CHEE: For 7-keto-DHEA, we have 2 yeses, 9 nos, and zero abstain.

DR. GULUR: Thank you, everyone. We will start the comments section. Dr. Carome, if you could?

DR. CAROME: Mike Carome. I voted no for similar reasons to the last one. I think there's just insufficient evidence establishing its long-term safety or effectiveness for the nominated uses.

DR. HOAG: Steve Hoag. In the previous one, I voted yes and I was on the fence. The data for this particular vote, I voted no. I thought just weighting the balance factors, this didn't meet the criteria for inclusion.

Also, this is probably a little bit more difficult compound to work with, to formulate. So the combination of those factors led me to vote no.

MS. JUNGMAN: Elizabeth Jungman. I also voted no. While there didn't seem to be significant safety concerns, there wasn't a long-term study there, and for weight loss, there were

approved alternatives. And for Raynaud's, the evidence of effectiveness was really anecdotal.

DR. BOGNER: Robin Bogner. I voted yes because I couldn't come up with a good reason to limit access to patients.

DR. PATEL: I voted no primarily based on the lack of evidence supporting its use. And what we've heard is anecdotal reports like Dr. Carome had mentioned earlier, without which published evidence, I don't think we could consider adding it to the list.

DR. DESAI: Seemal Desai. I voted no also. I was interested in this ingredient for its use in Raynaud's phenomenon, which I treat quite frequently, actually, as both Dr. Johnson and the nominator discussed this manifestation of lots of other skin diseases and other systemic issues.

But the fact that there was only one case report of which there was no way to elucidate the mechanism of action to improving the vasospasm is ultimately what led me to no, along with the lack of long-term safety data.

DR. GULUR: Dr. Wall on the phone?

DR. WALL: I voted yes. I'm not hearing a lot of, really, negatives for the safety. Granted, the evidence can be a little bit questionable, but I think that there may be a need for it in certain specific patients. Thank you.

DR. GULUR: Dr. Humphrey?

MR. HUMPHREY: William Humphrey. I voted no. I feel a little wishy-washy, given that I voted yes on the previous one. But I do agree with many of the statements that have already been made.

DR. GULUR: Dr. Davidson?

MS. DAVIDSON: I feel wishy-washy, too, but I voted no on this. After listening to the evidence, I thought there may be a little evidence to support, but then I learned that it was a different salt than was nominated.

I worried about decreasing patient access, but a quick search of the web reveals that you can get just about any salt or metabolite of DHEA as a dietary supplement, and perhaps that would still provide some access to patients that do show some

effects from it.

DR. GULUR: Padma Gulur. I voted no for reasons already stated, lack of long-term safety data. The efficacy data was really what convinced me on this one, anecdotal at best and, again, for a different salt altogether.

Dr. Venitz on the phone?

DR. VENITZ: This is Jurgen Venitz. I voted no, and I didn't feel wishy-washy about it because I do think there are major differences between the previous review and this one. There is no clinical trial to support efficacy or even the promise of efficacy.

There is maybe one, as far as I can tell you, a safety trial or something that you could construct to be a safety trial. So there is in my mind almost a total absence of safety and efficacy.

Adjournment

DR. GULUR: Thank you, everyone. With that, we will adjourn for lunch. We are slightly off schedule. I would request that everyone return at 1:45 so we can resume.

(Whereupon, at 12:54 p.m., the morning session was adjourned.)