FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Morning Session

Virtual Meeting

Wednesday, June 8, 2022

9:30 a.m. to 1:15 p.m.

Meeting Roster

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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

(9:30 a.m.)

Call to Order

DR. VAIDA: Good morning, everyone, and welcome. I would first like to remind everyone to please mute your line when you're not speaking. For media and press, the FDA press contact is Audra Harrison. Her email and phone number are currently displayed.

My name is Allen Vaida, and I will be chairing today's meeting. I will now call the June 8, 2022 meeting of the Pharmacy Compounding Advisory Committee to order. Dr. Takyiah Stevenson is the designated federal officer for this meeting and will begin with introductions.

Introduction of Committee

DR. STEVENSON: Good morning. My name is Takyiah Stevenson, and I am the designated federal officer for this meeting. When I call your name, please introduce yourself by stating your name and affiliation.

Dr. Robin Bogner?

DR. BOGNER: This is Robin Bogner. I'm from the University of Connecticut. Good morning, everyone.

DR. STEVENSON: Dr. Fensky?

DR. FENSKY: Good morning. I'm Tim Fensky, and I'm representing the National Association of Boards of Pharmacy. Thank you.

DR. STEVENSON: Ms. Fusco-Walker?

MS. FUSCO-WALKER: Good morning. This is Sandra Fusco-Walker with the Allergy and Asthma Network.

DR. STEVENSON: Dr. Gupta?

DR. GUPTA: Good morning. This is Dr. Anita Gupta from Johns Hopkins School of Medicine.

DR. STEVENSON: Dr. Gura?

DR. GURA: Good morning. I'm Kathy Gura, Boston Children's Hospital and Harvard Medical School.

DR. STEVENSON: Dr. McElhiney?

DR. McELHINEY: Hi. I'm Linda McElhiney, and I'm the team lead compounding pharmacist for Indiana University Health in Indianapolis.

DR. STEVENSON: Dr. Patel?

DR. PATEL: Good morning. This is Kuldip Patel from Duke University Hospital, representing hospitals and health system pharmacy.

DR. STEVENSON: Dr. Rebello?

DR. REBELLO: Good morning. This is Dr. Elizabeth Rebello, and I practice at University of Texas MD Anderson Cancer Center.

DR. STEVENSON: Dr. Serumaga?

DR. SERUMAGA: Good morning. This is Brian Serumaga, representing the United States Pharmacopeia.

DR. STEVENSON: Dr. Vaida?

DR. VAIDA: Good morning. This is Allen Vaida. I'm a former executive vice president for the Institute for Safe Medication Practices.

DR. STEVENSON: Dr. Calhoun?

DR. CALHOUN: Good morning. I'm Bill Calhoun from the University of Texas Medical Branch in Galveston.

DR. STEVENSON: Dr. Dmochowski?

(No response.)

DR. STEVENSON: Dr. Dmochowski, if you are trying to speak, you might be muted.

DR. DMOCHOWSKI: Roger Dmochowski, Vanderbilt University Medical Center.

DR. STEVENSON: Thank you.

Dr. Evans?

DR. EVANS: Good morning. This is Scott Evans. I am at the University of Texas MD Anderson Cancer Center.

DR. STEVENSON: Dr. Brian Green?

(No response.)

DR. STEVENSON: Dr. Vivian Lewis?

DR. V. LEWIS: Hello. This is Dr. Vivian Lewis, and I'm at the University of Rochester Medical Center.

DR. STEVENSON: Dr. David Margolis?

DR. MARGOLIS: Hi. This is David Margolis. I'm from the University of Pennsylvania, School of Medicine.

DR. STEVENSON: Dr. Bui?

DR. BUI: Good morning. This is Dr. Michael Bui from Pyxis Oncology.

DR. STEVENSON: Dr. Richard Green?

MR. R. GREEN: Good morning. This is Richard Green of Cardinal Health Nuclear and Precision Health Solutions.

DR. STEVENSON: I will now move on to the FDA participants.

Dr. Bormel?

MS. BORMEL: Good morning. This is Gail Bormel. I'm the director of the Office of Compounding Quality and Compliance at FDA.

DR. STEVENSON: Dr. Anderson?

(No response.)

DR. STEVENSON: Dr. Anderson, you may be on mute.

DR. ANDERSON: Yes. Sorry.

DR. STEVENSON: Sure. No problem.

DR. ANDERSON: Sorry about that. Yes, this is Kathleen Anderson, deputy office director for compliance and operations.

DR. STEVENSON: Gabrielle Cosel?

MS. COSEL: Good morning. This is Gabrielle Cosel. I'm the director of the Division of

Compounding Policy and Outreach in the Office of Compounding Quality and Compliance.

DR. STEVENSON: Rosilend Lawson?

(No response.)

Dr. Lawson?

DR. LAWSON: Good morning. This is Rosilend Lawson. I'm branch chief in the Office of Compounding Quality and Compliance.

DR. STEVENSON: Lori Bickel?

MS. BICKEL: Good morning. This is Lori Bickel. I'm a regulatory counsel in CDER's Office of Medical Policy.

DR. STEVENSON: Dr. Ganley?

DR. GANLEY: Good morning. I'm Charley Ganley. I'm the director of the Office of Specialty Medicine in the Office of New Drugs, in the Center of Drugs. Thank you.

DR. STEVENSON: Dr. Shetty?

DR. SHETTY: Good morning. This is Daiva Shetty. I'm associate director for the Pharmacy Compounding Review Team in the Office of New Drugs.

DR. STEVENSON: Dr. Kneeream?

DR. KNEEREAM: Good morning. This is Emily Kneeream. I'm a clinical analyst with the Pharmacy Compounding Review Team in the Office of New Drugs.

DR. STEVENSON: Dr. Wolfert?

DR. WOLFERT: Good morning. This is Madeline Wolfert. I'm a physician with the Pharmacy Compounding Review Team in the Office of Specialty Medicine, Office of New Drugs, FDA.

DR. STEVENSON: Thank you, everyone.

I will now turn it back to the chair.

DR. VAIDA: Thank you.

For topics such as those being discussed at this meeting, there are often a variety of options, some of which are quite strongly held. Our goal is that this meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the chairperson. We look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that 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 the breaks. Thank you.

Today we will discuss for bulk drug substances nominated for inclusion on the list of bulk drugs substances that may be used to compound drugs in accordance with Section 503A of the federal Food, Drug, and Cosmetic Act, also known as the 503A Bulks List: ammonium tetrathiomolybdate; enclomiphene citrate; ferric subsulfate; and glutathione.

For each of these four substances, we will hear presentations from FDA; have the opportunity

to ask clarifying questions; hear nominators' presentations, with the exception of ferric subsulfate; have the opportunity to ask clarifying questions; hold an open public hearing; and have committee discussion and voting.

The May 6, 2022 Federal Register notice identifies the uses FDA reviewed for each of the four bulk drug substances being discussed at this meeting. These uses reflect those for which adequate support was provided in the nomination. In addition, the nominations and the FDA evaluations for the bulk drug substances, which are included in the briefing document posted on FDA's website, identify 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' presentation 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 evaluation because the nominators either did not nominate those uses, dosage forms, and routes of administration, or they were not adequately supported.

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

Let us begin. We will now have Dr. Takyiah Stevenson read the Conflict of Interest Statement for this meeting's 503 Bulks List topics.

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration, FDA, is convening today's meeting of the Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. With the exception

of the National Association of Boards of Pharmacy, NABP; the United States Pharmacopeia, and the industry representatives, all members and temporary voting members of the committee are special government employees, SGEs, or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

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

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs

his or her potential financial conflict of interest or when the interest of a regular federal employee is not so substantial as to be deemed likely to affect the integrity of the services which the government may expect from the employee.

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

The committee will discuss four bulk drug substances nominated for inclusion on the 503A Bulks List. FDA will discuss the following nominated book drug substances and the uses that have been reviewed.

1) Ammonium tetrathiomolybdate for Wilson

disease; use of copper chelation therapy for the treatment of breast cancer, kidney cancer, prostate cancer, colorectal cancer, esophageal cancer, and malignant pleural mesothelioma;

2) enclomiphene citrate to increase serum testosterone, luteinizing hormone, and follicle-stimulating hormone, FSH, to normal levels in the treatment of secondary hypogonadism;

3) Ferric subsulfate for use as an astringent and hemostatic agent during minor surgical procedures; and

4) Glutathione for skin lightening; cystic fibrosis; asthma; chronic obstructive pulmonary disease; chronic lung disease; oxidative stress; reduction of the side effects of chemotherapy; inhibition of chemical-induced carcinogenesis; prevention of radiation injury; treatment of heavy metal poisoning, cadmium and mercury; acetaminophen toxicity; autism spectrum disorder; Alzheimer's disease; Parkinson's disease; major depressive disorder; schizophrenia; helicobacter pylori infection; human immunodeficiency virus infection;

tuberculosis; otitis media; peripheral obstructive arterial disease; anemia; diabetes; and septic shock.

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

This is a particular matters meeting during which specific matters related to the four bulk drug substances will be discussed. Based on the agenda for today's meeting and all financial interest reported by the committee members and temporary voting members, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) to Drs. Srinivasan Dasarathy and Kathleen Gura.

Dr. Dasarathy is only attending the ammonium tetrathiomolybdate topic. His waiver for that topic involves investment holdings in healthcare sector mutual funds with an aggregate value between $100,000 and $150,000.

Dr. Gura is attending all topics. Her waiver for those topics involve stock holdings in

an affected entity. The aggregate value of her stock is between $50,000 and $100,000.

The waivers allow these individuals to participate fully in today's deliberations. FDA's reasons for issuing the waivers are described in the waiver documents, which are posted on FDA's website at https://www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

Copies of the waivers may also be obtained by submitting a written request to the agency's Freedom of Information Division, 5630 Fishers Lane, Room 1035, Rockville, Maryland, 20857, or requests may be sent via fax to 301-827-9267.

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

We would like to note that Dr. Timothy Fensky is a representative member from the National Association of Boards of Pharmacy, NABP, and Dr. Brian Serumaga is a representative member from

the United States Pharmacopeia, USP. Section 102 of the Drug Quality and Security Act amended the Federal Food, Drug, and Cosmetic Act with respect to the Advisory Committee on Compounding to include representatives from the NABP and the USP. Their role is to provide the committee with the points of view of the NABP and the USP.

Unlike the other members of the committee, representative members are not appointed to the committee to provide their own individual judgment on the particular matters at issue. Instead, they serve as the voice of the NABP and USP entities with a financial or other stake in the particular matters before the advisory committee.

With respect to FDA's invited industry representative, we would like to disclose that Dr. Michael Bui and Mr. Richard Green are participating in this meeting as non-voting industry representatives, acting on behalf of regulated industry. Their role at this meeting is to represent industry in general and not any particular company. Dr. Bui is employed by Pyxis

Oncology and Mr. Green is employed by Cardinal Health Nuclear and Precision Health Solutions.

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

Thank you, and I will turn it back over to the chair.

DR. VAIDA: Thank you.

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

Dr. Bormel?

FDA Introductory Remarks – Gail Bormel

MS. BORMEL: Thank you, Dr. Vaida, and good

morning, everyone.

Again, my name is Gail Bormel, the director of the Office of Compounding Quality and Compliance, which is the FDA office primarily responsible for developing and implementing policies and compliance strategies to help assure the quality of compounded drugs. We recognize the importance of access to compounded drugs for patients who have a medical need for them. Our office aims to protect patients from the risk of poor quality or otherwise harmful compounded drugs.

I would like to welcome you to the 11th meeting of the Pharmacy Compounding Advisory Committee. Today, as you've heard previously, we will discuss bulk drug substances nominated for inclusion on the list of bulk drug substances that can be used in compounding human drug products under Section 503A of the federal Food, Drug, and Cosmetic Act, also known as FD&C Act.

This list is known as the 503A Bulks List. The substances that will be discussed are enclomiphene citrate; glutathione; ammonium

tetrathiomolybdate, ATTM; and ferric subsulfate. Some of these substances may be available in dietary supplements. As a reminder, the discussion today focuses on FDA's evaluation of these substances as bulk drug substances for use in human drug compounding under Section 503A of the Act, and is not intended to inform FDA's regulation of these substances in dietary supplements.

We also note the availability of a substance as a dietary supplement is not a criterion considered when evaluating a substance for inclusion on the 503A Bulks List. Dietary supplements are regulated under a different part of the FD&C Act and different considerations apply to the regulation of dietary supplements and drugs, including drug products compounded using bulk drug substances under Section 503A. For example, dietary supplements are intended for oral ingestion, while drugs may be intended for administration by numerous other routes of administration such as topically or by parenteral or intrathecal injection.

These different routes of administration raise very different considerations from a regulatory perspective, including safety considerations related to risk of contamination and considerations regarding systemic absorption.

The reviews conducted by the agency for bulk drug substances nominated for the 503A Bulks List follow the criteria described in FDA's regulations implementing Section 503A, which are separate and distinct from FDA's statutory and regulatory provisions governing the treatment of dietary supplements.

During this meeting, we will also discuss whether to add an entry for drug products containing lorcaserin hydrochloride to the list of drug products that have been withdrawn or removed from the market because such drug products, or components of such drug products, have been found to be unsafe or not effective. This list, known as the Withdrawn or Removed List, implements conditions under Section 503A and 503B of the FD&C Act.

As in previous meetings, we have scheduled time for the nominators to speak and time for an open public hearing after FDA's presentation on each of the four bulk drug substances. There will also be an open public hearing after the FDA presentation for lorcaserin hydrochloride.

I would now like to take this opportunity to provide you with an update on certain developments since the committee last met in June 2021. Some of these actions affect compounders under Section 503A of the FD&C Act such as state licensed pharmacies, federal facilities, and licensed physicians. Other actions affect those compounders known as outsourcing facilities that are regulated under Section 503B of Act. Finally, some of the actions affect compounders under both Section 503A and 503B.

Since our last PCAC meeting in 2021, the agency has worked to establish and revise guidance that affect compounders under Section 503A of the Act. In October 2021, FDA published a revised draft guidance concerning hospital and health

system compounding under Section 503A of the FD&C Act. The agency has also been working on policy documents that affect compounders under Section 503B of the Act, including those that advance their creation of the list of bulk drug substances for which there is a clinical need for use in compounding under Section 503B. That's known as the 503B Bulks List.

In January 2022, the agency issued a Federal Register notice, adding the first four bulk drug substances to the 503B list. The agency also determined that eight bulk drug substances will not be added to the list at this time, joining nicardipine hydrochloride and vasopressin. FDA has also issued compounding risk alerts to inform healthcare professionals, compounders, and consumers about risks associated with compounded drugs, including information on adverse events, outbreaks, or product quality.

In October 2021, the agency issued a compounding risk alert highlighting concerns with the compounding of drug products by medical offices

and clinics under insanitary conditions. In February 2022, FDA issued another alert warning healthcare professionals of the potential risks associated with compounded ketamine nasal spray. In addition, FDA announced that it intends to undertake notice and comment rulemaking related to a statutory provision regarding certain distributions of compounded human drug products and a standard memorandum of understanding -- that is an MOU -- between FDA and states.

The standard MOU is an agreement that is intended to address interstate distribution of inordinate amounts of compounded drugs and complaint investigations by a state regulator related to compounded drugs distributed outside the state. This falls within Section 503A of the Act.

FDA considers the standard MOU, published in October 2020, to be suspended. This means that during the rulemaking process, FDA will not enter into new agreements with states based on the standard MOU, and FDA does not expect the state that signed the standard MOU to carry out any

activities described in the MOU. In addition, the standard MOU will be updated based on the content of a final rule, and FDA intends to announce a new opportunity for all states to consider and sign the updated standard MOU.

Last, I want to turn to the Compounding Quality Center of Excellence, which continues to engage with outsourcing facilities, compounders, and other stakeholders to improve the overall quality of compounded drugs.

In 2021 and 2022, the Center of Excellence has offered several virtual instructor-led and self-guided trainings to support outsourcing facilities in their efforts to provide quality compounded drugs.

Also in September of 2021, the Center of Excellence held a virtual conference on the culture of quality, giving the opportunity to engage with FDA and learn about emerging trends and best practices to enhance the quality of compounded drugs. All of FDA's compounding policy documents, including our compounding risk alerts and the

Center of Excellence training opportunity, including those just discussed, appear on FDA's compounding website.

Again, I want to thank you for your participation on the Pharmacy Compounding Advisory Committee. We look forward to a productive meeting and to continuing to work together. This concludes my presentation, and I will turn it over to Lori Bickel.

FDA Presentation – Lori Bickel

MS. BICKEL: Thank you.

Good morning. I'm Lori Bickel. I'm a regulatory counsel in CDER's Office of Policy, and I have nothing to declare this morning.

I'd like to take a few minutes this morning to look at two ways investigational drug products can be used, either for research and IND or for treatment through expanded access. I'll go into a little detail about the requirements for all expanded access and the three categories. Finally, I'll take a quick look at some of the tools FDA has developed to help patients and their physicians

determine if expanded access is even an appropriate option and to streamline the process if it is.

To start, we're talking, again, about ways to access investigational drugs. Research on an investigational drug is done under an IND. To get to an approved drug, clinical trials are needed. They provide the data to determine the safety and efficacy of the product, among other things. However, a clinical trial isn't always an option, so in those cases, perhaps expanded access may be an avenue for treatment if appropriate conditions are met.

I'll start with the IND for research using an investigational drug, however, all of the key content of the IND submission that I'll cover are also applicable to expanded access submissions as well.

I break the components down into three categories for myself. The first is information about the investigator or physician. That can be submitted on either Form 1571-1572, which is the New Drug Application and Statement of the

Investigator, or Form FDA 3926, which is a new form created in 2016 for single-patient expanded access submissions. That will include the information about the investigator, or in the case of some expanded access, it's the treating physician of the patient, including all of their qualifications, CV, and things like that.

Moving on to the next bucket of information is information about the drug product: what is its chemistry, manufacturing, and controls information; what is the product identity, purity; how it will be distributed; and all of that type of information. Again, for some single-patient expanded access, a letter of authorization may be used to reference the chemistry, manufacturing, and controls information that is already on file with FDA in an existing IND.

Moving on to the next set of key content, other information about the drug is, obviously, the basic information on the safety and efficacy of the drug. The third set of information included in the IND is the information about the patient and the

proposed treatment; description of the disease or condition; and what the route of administration may be. Finally, all INDs will also need an informed consent form and IRB approval prior to beginning.

We're going to shift specifically to expanded access. In contrast to a clinical trial, which is primarily use of investigational drug for research, expanded access is the use of an investigational drug or biologic to treat a patient with a serious or immediately life-threatening disease or condition who does not have comparable or satisfactory alternate therapy.

Moving on to the basics of expanded access, the first thing I'd like to point out is actually the asterisk at the bottom of this slide. The sponsor and manufacturer of the investigational drug must agree to provide it to the patient for the expanded access use. Once that occurs, then there are three different types of expanded access.

The first is individual. That's a single patient, which is also involving a community physician with no past experience or involvement in

clinical trials as the sponsor/investigator of the IND. Individual patient expanded access use can also be emergency or non-emergency, depending on the situation

The second type of expanded access is intermediate size population. There's no set number for an intermediate size, but generally it's more than one and fewer than the number in a treatment IND or protocol. Then finally, the third type is a treatment IND, which is typically larger and widespread. A treatment IND or protocol usually occurs either after phase 3 or compelling phase 2 data analysis.

Now that we have the three types of expanded access, the next set of requirements apply to all three. As I've said, the patient must have a serious or immediately life-threatening disease or condition; there is no comparable or satisfactory available therapy; they aren't able to participate in a clinical trial; the risk-benefit analysis must show that the potential benefit justifies the potential risks; and finally, that providing

expanded access will not interfere with the product's development program.

In 2009, FDA published the final rule on expanded access. In 2016, we released a Q&A guidance which was revised in 2017 based on the 21st Century Cures Act. Both the guidance and the regulations include the general criteria for all types in each category of expanded access; the requirements for what information must be submitted; and finally, the safeguards for the patients, including IRB review, informed consent, and reporting requirements.

I'd also like to remind everyone at this point that all research done under IND -- as clinical trials, expanded access -- come with the full range of human subject protections, again, such as IRB review and informed consent.

Since the regs were published in 2009, FDA continues to take steps to make sure the program is known and that its criteria are known and followed so that the program is used appropriately and within its intended scope. That included creation

of Form FDA 3926 in 2016. Prior to that, again, some single-patient access was conducted by community physicians who didn't have prior experience with INDs. However, before 3926, they had to use Form 1571 and 72, which is the same form as a commercial IND. That's part of the reason FDA heard stakeholder input and created the streamlined Form 3926 for single-patient expanded access INDs.

At the same time, FDA updated the guidances and our website. We've had an ongoing collaboration with the Reagan-Udall Foundation to launch various tools to assist users, again, in determining if expanded access is appropriate, and then help to walk them through the process if it is.

FDA's Oncology Center of Excellence launched Project Facilitate in 2019, which is also a program to help provide one-on-one assistance through the process. Finally, FDA has an internal expanded access coordinating committee. It's an internal work group made of FDA staff to meet monthly and discuss expanded access and the program.

Here is a screenshot from FDA's website. Again, it's a rather user-friendly website. There's also a link to a series of FDA-produced informational videos. We won't have an opportunity for questions today, so I wanted to be sure to provide the contact information for any questions that members of the committee or the public may have about expanded access or INDs, and here are links to the regulations and guidances that I mentioned.

Thank you all for the chance to speak with you this morning. I'll now hand it back to Dr. Vaida, the chairperson.

DR. VAIDA: Thank you.

We will now proceed with FDA presentations, starting with enclomiphene citrate from Dr. Madeline Wolfert.

FDA Presentation – Madeline Wolfert

DR. WOLFERT: Good morning. My name is Madeline Wolfert. I am a physician with the Pharmacy Compounding Review Team in the Office of New Drugs, and I will be presenting enclomiphene

citrate. I would like to recognize the entire evaluation team, as well as the contribution of many other FDA colleagues. Our special thanks to the Division of Urology, Obstetrics, and Gynecology in OND.

Enclomiphene citrate, which I'll refer to as enclomiphene, was nominated for inclusion on the list of bulk drug substances that can be used to compound drug products in accordance with Section 503A of the FD&C Act, known as the 503A Bulks List. Enclomiphene was evaluated for the use to increase serum testosterone, LH, and FSH to normal levels in the treatment of secondary hypogonadism. The proposed dosage forms are oral capsules or tablets 12.5, 25, and 50 milligram.

The criteria we consider in our evaluation for the 503A Bulks List are physical and chemical characterization, nonclinical and clinical safety, available evidence of effectiveness or lack of effectiveness, and historical use in compounding.

Enclomiphene citrate is a small molecule and has no USP monograph. It can be made by separation

from the mixture of geometric isomers, enclomiphene and zuclomiphene. The mixture of these two isomers is clomiphene citrate, which I'll refer to as clomiphene. Unlike enclomiphene, clomiphene has a USP monograph and is the active ingredient in an approved drug. Based on the USP monograph, its enclomiphene content is 50 to 70 percent.

Clomiphene is stable when stored at room temperature and protected from light. Since enclomiphene is one constituent of clomiphene isomeric mixture, it's expected to be stable when stored under similar conditions.

Enclomiphene can be characterized by common tools and techniques. It is slightly soluble in water. The impurity profile is expected to be similar to clomiphene with other likely impurities, which are unlikely to be toxic if adequately controlled. In conclusion, enclomiphene is a well-characterized small molecule expected to be stable under ordinary storage conditions when protected from light in the proposed form.

Now I'll discuss nonclinical information.

Enclomiphene is a selective estrogen receptor modulator, SERM, which acts by blocking the estrogenic suppression of the HPG axis. As a result, the pituitary secretes more LH and FSH, which stimulates testes to produce more testosterone. Animal studies suggest that enclomiphene can treat secondary hypogonadism by increasing testosterone levels.

Data for the nonclinical programs are from the European Medicines Agency, EMA, 2018 public report that reviewed enclomiphene for marketing authorization. Oral dosing in rodents showed rapid absorption and dose-related increase in plasma levels. Repeat-dose toxicity in rats found no minimum no adverse effect level, reduced body and organ weight, and histopathological findings in the prostate, testes, seminal vesicles, and kidneys. In dogs, deaths in high-dose animals were related to hepatotoxicity. Other findings were organ weight changes and ophthalmic abnormalities.

Enclomiphene was negative in a battery of genotoxicity assays. For developmental and

reproductive toxicity, 200 mg per kg resulted in mortality in male mice. Lower doses were associated with altered sperm parameters, increased resorptions, and post-implantation loss. For carcinogenicity, findings from studies in mice and rats concluded enclomiphene is not carcinogenic.

To conclude, the nonclinical toxicity profile of enclomiphene reflects its exaggerated pharmacological action as a SERM. Reproductive adverse findings include decreases in organ weight and histopath findings. The potential nonreproductive target organs include liver, kidneys, and eyes. It is not genotoxic or carcinogenic.

Now we'll discuss clinical PK. Oral enclomiphene is rapidly absorbed with a half-life of 10 hours. Max serum concentration is 2 to 3 hours after intake. Excretion is mainly in feces. Cmax increased in a greater than dose proportional manner from 12.5 to 25 milligram, and a less than dose proportional manner from 25 to 50 milligram. The main metabolite appears to be

4 hydroxy enclomiphene.

For clinical safety, we considered these sources: FDA Adverse Event Reporting System, FAERS; published clinical trials and clinicaltrials.gov; and other safety information.

In terms of clinical trials, Kim, et al. published phase 3 trials in patients with secondary hypogonadism. They compared enclomiphene 12.5 milligram or 12.5 uptitrated to 25 milligram and topical testosterone. Here are the adverse events, AEs, reported; 2 deaths, which investigators considered unlikely to be due to the study drug. In the 25 milligram and testosterone groups, a patient discontinued due to high hematocrit or hemoglobin. In the 25-milligram group, a patient also discontinued due to high PSA.

Another trial in patients with secondary hypogonadism compared enclomiphene 12.5 and 25 milligrams, topical testosterone, and placebo. AEs in enclomiphene 25 milligrams included inability to climax and loss of sensation during intercourse and GI symptoms. These were considered

possibly related to the study drug. Both patients discontinued.

Another 2014 trial compared enclomiphene and topical testosterone. AEs included mildly increased estradiol and headaches. In a safety study which evaluated enclomiphene 12.5 milligram and 12.5 uptitrated to 25 milligram, serious AEs are seen in the table and non-serious AEs are listed below. Serious AEs included cardiac and thromboembolic events such as bradycardia; chest pain; TIA; hypotension; atrial flutter; pulmonary embolism; and deep vein thrombosis. Non-serious AEs included hot flushes, muscle spasms, and headaches.

The EMA reviewed enclomiphene for marketing authorization to treat secondary hypogonadism and concluded that safety was not sufficiently demonstrated. Most frequent AEs were headache, hot flushes, nausea, and muscle spasm. Those leading to discontinuation were blurred vision, muscle spasm, headache, and aggression. Incidence of cardiac and thromboembolic events in the

enclomiphene group was also slightly increased compared to patients treated with testosterone.

Also from the EMA report, cataracts were reported in nonclinical studies. EMA said that data did not provide conclusive evidence that enclomiphene caused new or progression of existing cataracts but recommended that ocular safety monitoring be included in a risk management plan. And finally, EMA considered PK data incomplete to inform dose adjustments in elderly patients, renal and hepatic impairment, and to exclude the possibility of a unique metabolite of significance.

To conclude, safety concerns include cardiac and thromboembolic events; elevated estradiol; increased PSA; and increased hematocrit, with long-term safety data lacking. PK data are limited, including information on dose adjustments for renal or hepatic impairment. There are FDA-approved therapies that meet established criteria for safety and efficacy, and they are labeled accordingly to inform their safe use.

I'll now switch gears to provide a brief

overview of hypogonadism. It's a clinical syndrome that results from failure of testes to produce physiological concentrations of testosterone and/or a normal number of sperm due to pathology in the HPG axis. It's classified as primary or secondary.

Secondary hypogonadism, which is what we'll focus on, is dysfunction arising from the level of the hypothalamus or pituitary. Men have low testosterone and low or inappropriately normal LH and FSH. It's also called hypogonadotropic hypogonadism. Diagnosis is based on signs and symptoms and low testosterone levels. Definitions of low testosterone vary, but the AUA recommends diagnosis below 300. Signs and symptoms include those seen on this slide.

Treatment depends on underlying etiology and goals for fertility. Products approved for treatment include testosterone and hCG. Because exogenous testosterone can impair spermatogenesis, there's interest in non-testosterone alternatives for men such as hCG or SERMs like enclomiphene.

No FDA-approved drugs contain enclomiphene

as active ingredient. Repros submitted an NDA for enclomiphene to treat secondary hypogonadism in fertile men. In 2015, Repros announced a complete response from FDA that the design of phase 3 studies was not adequate to demonstrate clinical benefit and concerns regarding study entry criteria, titration, and bioanalytical method validation.

In 2016, Renable Pharma applied to EMA for marketing authorization of enclomiphene to treat secondary hypogonadism. As discussed in previous slide, in 2018, EMA refused marketing authorization, determining that safety and efficacy were not sufficiently demonstrated.

Now I'll present information on effectiveness of enclomiphene for secondary hypogonadism. A small trial compared enclomiphene 25 milligram and topical testosterone to evaluate changes in hormone levels and seminal parameters. Testosterone levels increased in both groups, but two men in the enclomiphene group did not achieve testosterone greater than 300 during treatment. LH

and FSH increased in the enclomiphene group.

In another trial to evaluate effects on LH and total testosterone, enclomiphene was compared to transdermal testosterone. Testosterone levels increased in all groups with greater variability in the transdermal testosterone group. LH and FSH increased in enclomiphene groups.

Wiehle, et al. compared enclomiphene 12.5 and 25 milligrams, topical testosterone, and placebo. Testosterone increased in all active treatment groups. LH and FSH increased in enclomiphene groups and decreased in topical testosterone group. Another trial compared the effects of enclomiphene, topical testosterone, and placebo. Testosterone levels increased in active treatment groups and LH and FSH increased in enclomiphene groups.

Phase 3 trials compared enclomiphene 12.5 milligram, 12.5 uptitrated to 25 milligram, topical testosterone, and placebo. Authors found testosterone increased in all active treatment groups. LH and FSH increased with enclomiphene and

decreased in the topical testosterone group. After cessation of treatment, testosterone levels in enclomiphene groups remained higher than baseline for 7 days.

If you recall on a previous slide, I mentioned that clomiphene is a mixture of enclomiphene and zuclomiphene. A review by Earl and Kim noted the following: that enclomiphene maintains the androgenic effect of clomiphene without the estrogen agonist effect of zuclomiphene, but the effects of zuclomiphene are not fully understood; that enclomiphene preserves sperm concentration compared to testosterone replacement, which I'll address on the next slide; although the evidence is weak, studies suggest that the side effect profile is not significantly worse than testosterone or clomiphene but needs further research to confirm this hypothesis; that enclomiphene achieved comparable testosterone levels to testosterone replacement while increasing LH and FSH; but that further studies are necessary to fully characterize the impact on subjective

symptoms of hypogonadism and to fully characterize its AE profile.

An FDA guidance in May 2018 provides recommendations for establishing clinical effectiveness for drugs intended to treat secondary hypogonadism attributed to nonstructural etiologies. It incorporates advice received at the Bone, Reproductive, and Urologic Drugs Advisory Committee December 2016 meeting.

The guidance states that it's unclear whether increasing testosterone in this population confers clinical benefit. Trials should show clinically meaningful improvement in at least one symptom or sign of secondary hypogonadism.

In addition, FDA does not consider that changes in semen parameters alone are sufficient to establish efficacy since the intent of the drug is to improve fertility, and improvement in semen parameters does not ensure fertility. The EMA also concluded that normalizing testosterone was not sufficient to conclude translation into clinically meaningful benefits. Note that enclomiphene trials

did not evaluate improvement in hypogonadal symptoms or quality of life.

In conclusion, while studies may suggest that enclomiphene may increase testosterone with an increase in LH and FSH, it's unclear whether increasing testosterone in secondary hypogonadism confers clinical benefit. Clinical trials did not demonstrate clinically meaningful improvement in symptoms or signs of hypogonadism. There are FDA-approved therapies with established efficacy.

Here's what we found on historical use in compounding. There's insufficient information on length of use. It's been studied in follicular development, ovulation induction, and secondary hypogonadism, but unclear whether the products used were compounded. Based on advertising information, it's discussed for treatment of male hypogonadism, but there are insufficient data on extent of use. It's not recognized in the European or Japanese pharmacopoeias.

After considering the information currently available, a balancing of the criteria weighs

against enclomiphene citrate being added to the 503A Bulks List. Thank you very much. This concludes my presentation.

DR. VAIDA: Thank you, Dr. Wolfert.

We will now take clarifying questions for FDA presenters. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member. [Inaudible – audio lost.]

(No response.)

DR. VAIDA: I don't see any raised hands for the FDA presenter, so why don't we move on to the nominator presentations, and then we will have an

opportunity to ask questions of the FDA and the nominators.

We have two presentations from Drs. Elsaied and Masterson, who are speaking on behalf of Empower Pharmacy. Please proceed.

Nominator Presentation – Marwa Elsaied

DR. ELSAIED: Good morning. My name is Marwa Elsaied, and I'm the director of medical affairs for Empower Pharmacy. I'd like to take a moment to thank the FDA for hosting this virtual meeting.

I'd like to start by looking at the prevalence of hypogonadism. A cross-sectional survey conducted discovered that about 12 percent of the study population was diagnosed, indicated by low serum testosterone levels and non-elevated LH, as you can see on the image. The HIM study evaluated 2,000 men, and some, just under 40 percent, were hypogonadal.

The FDA briefing document acknowledges that enclomiphene has been studied for several decades for secondary hypogonadism. Enclomiphene is the

main isomer making up about 62 percent of an already FDA-approved drug, clomiphene. Enclomiphene is the estrogen antagonist with a half-life of hours, while zuclomiphene is the estrogen agonist with a half-life of weeks.

Clomiphene is actually a group for ovulatory dysfunction due to the estrogenic isomer, which is counter-intuititive for treatment in men. A preclinical study done on mice found that zuclomiphene disrupted sperm production, while enclomiphene preserved it. The same study found that testicles, epididymis, seminal vesicles, and mice overall had a decrease in weight in the zuclomiphene group when compared to enclomiphene. Another preclinical study done in baboons found that zuclomiphene did not impact testosterone levels and increased total cholesterol by 22 percent, while enclomiphene decreased levels by 8 percent.

The FDA briefing document mentions a preclinical study done on dogs where dose reductions were needed due to morbidity. It's

worth mentioning that the dose used here was very high at 40 milligrams per kilogram per day, while the average human dose is just 12.5 to 25 milligrams daily.

As with all FDA-approved testosterone therapies, thromboembolic events are noted. The EMA report of 2018 mentioned the same facts in their document. At a presentation at the annual Sexual Medicine Society of North America, Pastuszak, et al. analyzed 11 prospective studies and found that hemoglobin and hematocrit were higher in men on testosterone gel than men on enclomiphene.

In the FDA briefing document, it states that it's unclear whether increasing testosterone concentrations equates to clinical effectiveness, however, the Endocrine Society guidelines define hypogonadism as a failure to produce a normal number of sperm, and goes on to mention that the recommended treatment is testosterone therapy. More importantly, testosterone therapy should not be used for men planning on fertility. So not only

does enclomiphene raised testosterone levels, it does not impair sperm production and can be used for men wishing to preserve their fertility.

The FDA also mentioned that parameters on semen analysis are not tests of fertility. The American Urological Association and American Society of Reproductive Medicine states that semen analyses are to be used for male fertility. The WHO laboratory manual states the importance of semen examination, as it helps to assess reproductive function and the appraisal of fertility function; so semen parameters are an important part of the ability to conceive, and therefore by extension fertility.

In 2021, Keihani, et al. conducted a study to determine what semen parameter thresholds were associated with an earlier time to conception in couples undergoing fertility evaluation. Over 6,000 men from subfertile couples were followed for 5 years to capture this conception data. Improvement in semen concentration, progressive motility, and total sperm count were all associated

with a higher conception rate and with an earlier time to conception, about half the time for other patients with lower cut-off parameters.

The FDA mentions that human chorionic gonadotropin, or hCG, can be used for secondary hypogonadism, but this drug has been on allocation and back order for months, causing patient access issues. The other treatment option, exogenous testosterone, appears to have multiple risk factors that are not seen with enclomiphene, including supranormal testosterone levels, suppressed spermatogenesis, and suppressed testicular function.

Most important, patients are seeing improvement in their signs and symptoms of hypogonadism with enclomiphene therapy. Comments pulled from the FDA docket show these patient-reported outcomes.

Our first patient here states that he has seen incredible beneficial effects in his mental health, libido, physical well-being, and his cholesterol and blood pressure levels have also

improved since starting treatment. Our second patient mentions that enclomiphene therapy has provided him with a marked improvement in his mood and his energy, and a third patient thinks that he has had much more energy, will power, and sex drive since starting enclomiphene.

Enclomiphene is part of an already FDA-approved drug. Exogenous testosterone therapy impairs sperm production while enclomiphene does not; and most important, patients' comments on the docket illustrate the importance in signs and symptoms of hypogonadism. For the last two years, Empower Pharmacy has had over 400 providers write for enclomiphene citrate. Over 19,000 prescriptions and about 727,000 capsules have been dispensed, and to our knowledge, no providers or patients have reported adverse events.

I will now hand it over to Dr. Masterson of the University of Miami to speak on clinical efficacy. Thank you.

Nominator Presentation – Thomas Masterson

DR. MASTERSON: Hi. Good morning. I'm

Dr. Thomas Masterson from the University of Miami. I'm a board-certified urologist and fellowship trained in male reproductive and sexual medicine. I do not have a financial relationship with Empower Pharmacy, however, I do prescribe their medication.

Clomiphene citrate is the selective estrogen receptor modulator and has two stereoisomers. The cis isomer is an estrogen receptor agonist with a long half-life, and we believe this is responsible for many of the undesirable side effects of clomiphene; whereas the trans isomer called enclomiphene has a shorter half-life and acts as an estrogen receptor antagonist, which increases endogenous LH and FSH production. This is the clinically useful isomer that has the effects on testosterone production and spermatogenesis.

The 25-milligram dose reaches its serum peak within 2 to 3 hours, and despite the short half-life, it leads to an increase in LH and FSH for nearly 7 days. In phase 1 animal studies comparing the isomers, enclomiphene had a significantly greater effect on serum testosterone

levels. In a phase 2 human trial of 12 hypogonadal men comparing the effect of testosterone to enclomiphene on sperm, exogenous testosterone decreased sperm count while enclomiphene increased sperm count.

These results were later supported by a second phase 2 study comparing exogenous testosterone to enclomiphene in 73 hypogonadal men. Again, both medications increased serum testosterone levels, but the enclomiphene maintained sperm count.

Lastly, in a phase 3 randomized-controlled trial of 265 overweight men comparing testosterone gel to enclomiphene, both medications increased serum testosterone levels, however, the testosterone gel significantly decreased sperm count; so in summary, enclomiphene increases serum testosterone while maintaining sperm count. Unfortunately, as with any drug, there are side effects, and enclomiphene seems to be associated with abdominal discomfort, headaches, and increased estrogen.

Male factor infertility is common, and there are very few medications available to assist us. hCG is a direct analog of LH, and this increases endogenous testosterone production, however, this drug is becoming more difficult to obtain and expensive. We have therefore been using enclomiphene as a means to increase LH production since November of 2001. We've been using this in men with low testosterone, hypogonadal symptoms and oligospermia, meaning low sperm count, and to date we have treated around 160 patients.

Now, we have not had a chance to formally study enclomiphene in our clinics, and we were not really anticipating having this meeting, so we don't have the complete data on 160 patients, but I do have some of our clinical data available to support enclomiphene's effectiveness in increasing serum testosterone.

It also increases intratesticular testosterone, and this is represented by 17-OHP on the chart, and please note that there was no significant change in estrogen in our patient

group. We also observed that despite these increases in serum testosterone, sperm counts and motility also increased.

Now, we want to keep in mind that when giving exogenous testosterone, which is the approved treatment for low testosterone, sperm counts do decrease. When looking at symptom improvement, there are no AUA recommended validated surveys for monitoring hypogonadism, so this is clinical self-report. But clinically we found that nearly two-thirds of our patients had complete improvement in symptoms, 10 percent had improvement in two or less symptoms, and 20 percent had no improvement in symptoms.

Lastly, we observed that there were very few side effects of enclomiphene, and in fact when reviewing the charts of our last 69 patients, 22 of them were actually switched from clomiphene citrate to enclomiphene citrate due to treatment-related side effects. So in conclusion, enclomiphene appears to increase serum testosterone, preserve semen parameters, and has minimal side effects, and

thank you for your time.

Clarifying Questions from the Committee

DR. VAIDA: Thank you, Dr. Masterson.

We'll now take clarifying questions for the nominator presenters. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you've asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it would be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

So far, we have one question from Dr. McElhiney.

DR. McELHINEY: Yes. This is for Dr. Masterson.

This enclomiphene, is it going to be a treatment that's used long term, or is it mainly used to increase infertility in males --

DR. MASTERSON: Thank you. That's a great question.

Dr. McELHINEY: -- short term?

DR. MASTERSON: Yes, a great question.

It depends on patient goals of care. Many of the patients that we're seeing come in with both problems, both low testosterone and have a fertility issue, and in that situation, this is where we use enclomiphene. We have another group of patients of younger hypogonadal men who, even though they may not be interested in fertility at this moment, if they have fertility concerns in the future, we will place them on enclomiphene long term.

DR. McELHINEY: Thank you.

DR. VAIDA: Alright.

Dr. Lewis?

DR. V. LEWIS: Hi. This is Dr. Lewis. I too am curious about the efficacy of using this

medication for enclomiphene for infertility, and I'm pretty surprised there really aren't any studies. When you talk about using it long term, what do you mean? And I guess, is there any evidence that it might be different than using clomiphene long term for infertility?

DR. MASTERSON: I'll answer that; Tom Masterson again.

For most patients, when we say long term, we're meaning generally longer than 6 months to 1 year. Again, depending on the indication, if these are patients who have a fertility concern, it depends on their fertility plan on the side, meaning what's happening with the female partner. For some, it's trying to maintain sperm count at a level where they can do intrauterine insemination or IVF; for others, they're attempting naturally.

Again, the FDA-approved medication for the treatment of low testosterone would be to put them on testosterone. Not presented in this data, but men on injection therapy, men on gels, up to 60 percent of them become azoospermic on those

therapies, so it's not just a decrease; it's actually making them infertile. So enclomiphene kind of fits into a niche where it can actually increase testosterone, improve some of those hypogonadal symptoms, and at least maintain sperm counts.

DR. V. LEWIS: Okay. Thank you.

Maybe for the FDA, just as a follow-up, I understand and agree that it's kind of a funny endpoint to say, well, it changes the labs parameters without some clinical indication.

For males then, you're talking about using this medication, or you want to consider using it for medication, has FDA discussed with any sponsors what kind of studies would be needed to show efficacy for treatment of male infertility when it's due to secondary hypogonadism with low testosterone levels, and what would that entail? How difficult would those studies be?

DR. VAIDA: Dr. Lewis, at the current time, we're just taking questions for the nominators, but in a few minutes we will have the opportunity to

take questions with the FDA also. So if you could hold that question for the next few minutes, please?

DR. V. LEWIS: Okay. Thank you.

DR. VAIDA: Yes. I have a question myself, first with Dr. Elsaied.

Did you comment that there were thousands of prescriptions that were compounded for enclomiphene?

DR. ELSAIED: Yes, correct. Those were internal reports, and we've dispensed over 19,000 prescriptions in the last two years.

DR. VAIDA: Okay. And that was just from your pharmacy?

DR. ELSAIED: Correct.

DR. VAIDA: Alright.

For Dr. Masterson, do you use several compounding pharmacies or you just use one compounding pharmacy for your study group?

DR. MASTERSON: We have different providers within our institution. Several of us use Empower, but there are some other local compounding

pharmacies we use as well.

DR. VAIDA: Okay. Thank you.

I don't see any more raised hands, and I would like to state for the record that there are no open public hearing speakers for this topic. So we will now have the opportunity to take any remaining clarifying questions for all the enclomiphene citrate presenters.

Once again, please use the raise-hand icon to indicate you have a question, and remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

As a gentle reminder, it will be helpful to acknowledge the end of your question with a thank you, and the end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

We have a question from Dr. Patel.

DR. PATEL: Thank you, Dr. Vaida.

Can you hear me ok?

DR. VAIDA: Yes.

DR. PATEL: My question is for Dr. Masterson with regard to the data that was presented.

Dr. Masterson, you mentioned there were 160 patients, I believe, that were looked at, that you've created thus far. Since it was a retrospective analysis, I was wondering how you or the team decided to select looking at 30 -- I think it was 30 patients that you looked at to collect data, and when I looked into the details, it looks like for the efficacy part, it may have been roughly 53 or so. Then for the safety, you had mentioned that 69 patients didn't have any side effects -- or the target review involved 69 patients.

I was just wondering how the patient selection was determined and which specific charts to look at vs not. Since it's a retrospective analysis, there's obvious concern for variability in how patients that didn't get included, what may

have occurred with regard to efficacy or safety.

If you could just comment on that, I would appreciate it. Thank you.

DR. MASTERSON: Yes. Thank you for your question.

When we were asked to present, we did not start prescribing this medication with the intent of performing any sort of prospective study, so we basically went through all of the charts of patients who had prescribing data and saw who had follow-up information.

Our typical practice pattern is once we start patients on this medication, it takes a minimum of 3 months to have any effect on sperm count, so we usually see patients back within the 3-to-6-month mark. Since we started using the medication, only last November 2001, we just don't have robust follow-up data to present here today.

So just to summarize that, we looked at all charts and really just presented here whoever had serum data that we could present, symptom data, and sperm count data. Thank you.

DR. PATEL: Thank you.

DR. VAIDA: Dr. Lewis?

DR. V. LEWIS: Hi. Thank you.

DR. VAIDA: Dr. Lewis?

DR. V. LEWIS: Yes. Can you hear me?

DR. VAIDA: Yes.

DR. V. LEWIS: Thank you. I'll just restate my question for the FDA.

What would it take to show clinical efficacy of enclomiphene for treating infertile men in this population; for example, numbers of patients and what endpoints would you be looking at? Thank you.

DR. KAUL: This Dr. Kaul. Can you hear me?

(No response.)

DR. KAUL: Hello?

DR. VAIDA: Yes.

DR. KAUL: This is Suresh Kaul. I'm the team leader for the Division of Urology, Obstetrics, and Gynecology. I would like to respond to Dr. Lewis' question, an excellent question.

We have a guidance from 2018, an FDA issued

guidance, that Dr. Madeline Wolfert earlier alluded to. That guidance clearly says changes in semen parameters are not sufficient alone for establishing efficacy of these drugs since the intent of the drug is to improve fertility and improvement of semen parameters does not ensure fertility.

I would further go and answer Dr. Lewis' question that this has come up many times, and this has been discussed with the sponsors. The ultimate endpoint of this clinical benefit would be clinical pregnancy, but no company so far has been willing to go for that study.

DR. V. LEWIS: Okay. Thank you. That answers my question.

DR. KAUL: Thank you.

DR. VAIDA: Dr. Lewis, do you have any further questions? Okay.

This is Allen Vaida. I just have a question of the FDA. I thought in your presentation you said that there were no reported compounded products from 2017 to 2021, yet Empower Pharmacy

said that they've compounded 19,000 prescriptions.

Is that just something that you may not have the correct information on?

DR. TAYLOR: This is Ann Taylor from the Office of Compounding Quality and Compliance. I think Tracy Rupp would like to respond to that question.

DR. RUPP: Yes. Thanks, Ann.

Hi, everyone. This is Tracy Rupp from the Office of Compounding Quality and Compliance, and you're correct that in the report, in the historical use section, we noted that we did not find any reports of compounded enclomiphene products.

This is from the Outsourcing Facility Product report, so this is specifically related to what 503B compounders report in their product reports, and it's voluntary. It's required reporting, but we can only report what is reported to us. In the reports that are submitted every 6 months, we did not receive any reports of compounded products by outsourcing facilities for

enclomiphene.

DR. VAIDA: Okay. Thank you.

Rebecca McKinnon, do you have a question?

DR. McKINNON: Rebecca McKinnon.

Chairman Vaida, Dr. Ganley from OND would like to be recognized for a comment.

DR. VAIDA: Yes. Sure. Go ahead.

DR. GANLEY: Hi. Thank you. I just wanted to follow up on a question that Dr. Lewis asked of Dr. Masterson with regard to the use of the FDA-approved drug vs the compounded drug. I don't think he answered that.

Does he use FDA-approved drugs to treat male infertility, and if not, why not?

DR. MASTERSON: Yes. Great question. Clomiphene citrate is FDA approved, though it is not FDA approved for the indication of male fertility. It's an off-label use. The reason we switched over to enclomiphene, enclomiphene citrate, was really due to side effects. We've observed that there were less side effects in the enclomiphene compared to clomiphene citrate.

DR. GANLEY: Thank you. I guess the other question, is the only route of administration orally?

DR. MASTERSON: Yes, clomiphene/enclomiphene are both oral drugs.

DR. GANLEY: So you're not aware of it being compounded in an injectable or a topical form?

DR. MASTERSON: I'm not aware, and we are not using.

DR. GANLEY: Thank you. I'm done.

DR. VAIDA: Okay.

Any further questions?

DR. CALHOUN: This is Dr. Bill Calhoun from University of Texas. I have a question for the agency, a broader question that relates to the issue of enantiomers.

There are two isomers of this compound. It's my understanding that the general guidance of the agency is that there are two isomers; that the active isomer is preferred, and that racemic mixtures, or mixtures of isomers, are generally --

DR. STEVENSON: Hello. I'm sorry to

interrupt. This is Takyiah Stevenson.

Dr. Calhoun, can you hear me?

DR. CALHOUN: Yes.

DR. STEVENSON: Yes. I do apologize. I just want to remind you that you are actually participating in the glutathione topic. You can certainly ask clarifying questions during that topic. We're still in the enclomiphene citrate topic. Sorry to interrupt.

DR. CALHOUN: Okay. Yes, this was just a more general question, but I understand. Thanks anyway.

DR. STEVENSON: Okay. You're welcome. Sorry.

DR. VAIDA: Dr. Patel, do you have another question?

DR. PATEL: I do. Thank you. This question is for Dr. Wolfert, so for the FDA.

From the data presented, there were two companies that conducted studies. My question was whether in both of those trials, where they ended up essentially demonstrating no clinical benefit,

what were the key endpoints that there were looking at? Was it clinical pregnancy or were they looking at markers?

DR. WOLFERT: Thank you for your question. In the EMA report, the markers that were discussed in phase 2 and phase 3 trials were similar to what I presented in the publications I shared; total testosterone, LH/FSH, and semen parameters. Clinical pregnancy was not discussed in the EMA report, to my knowledge. Thank you.

DR. PATEL: Thank you. That is all for my question.

DR. VAIDA: Dr. Lewis, do you have a follow-up question?

DR. V. LEWIS: Yes. This is Dr. Lewis. I do have another question. I'm not sure to whom I should direct it. It's probably the non-FDA presenters.

I'm a reproductive endocrinologist, and I've treated many, many infertile couples, and clomiphene citrate is extremely widely used off label. I'm just curious; what is the cost

differential between clomiphene citrate, generic form let's say, and enclomiphene?

Also, are there any offshore pharmacies that you're aware of that produce enclomiphene that are in use in the United States?

DR. TAYLOR: This is Ann Taylor from the Office of Compounding Quality and Compliance. Tracy Rupp would like to respond to this, as well as make a comment regarding the earlier statement.

DR. RUPP: Yes. Hi. This is Tracy Rupp from the Office of Compounding Quality and Compliance. I'd just like to note that we can't address cost issues, but we're not aware of facilities outside the United States producing compounded products for use in the United States. I believe that was your question.

The other point that I wanted to clarify was earlier Dr. Vaida asked about the comment in the evaluation about outsourcing facility product reporting data and how there were no reported compounded drug products containing enclomiphene citrate. So that is true; there were no product

reports for outsourcing facilities in that time period.

However, in the evaluation, we also do discuss that we did find reports of enclomiphene use on the websites of medical clinics and compounding pharmacies in the United States, so we are aware of certain 503A facilities, like pharmacies and so forth, producing compounded enclomiphene citrate. Thank you.

DR. VAIDA: Okay. One final question due to time.

Dr. McElhiney, did you have --

DR. McELHINEY: Yes. This is Linda McElhiney. They mentioned that hCG was the commercial approved product for infertility in place of enclomiphene. Dr. Masterson mentioned that it's on and off back order a lot. And I know there was a controversy about compounding hCG.

So compounding pharmacies, when hCG is on back order, are they allowed to compound hCG injections or would enclomiphene be the only alternative to that? Thank you.

DR. MASTERSON: Hi. This is Dr. Masterson. I'm not sure if that question was directed at me or not, but similarly, hCG is also not FDA approved for the treatment of male fertility. It's another off-label use of hCG.

DR. VAIDA: Any comment from the FDA?

DR. TAYLOR: Thank you. This is Ann Taylor. Gaby Cosel would like to respond to your question.

MS. COSEL: Yes. Can everyone hear me?

Just regarding the question about hCG, hCG is a biologic product. Section 503A and 503B, biological products are not eligible for the exemption for compounded drugs under Section 503A and 503B; so just to clarify that those sections don't provide a pathway for compounding with hCG. We do have a guidance on the mixing and/or repackaging of biological products outside the scope of an approved biologics license application, which provides certain pathways for manipulating approved products.

DR. VAIDA: Dr. Wolfert?

DR. WOLFERT: Yes. Thank you. This is

Dr. Wolfert. I just wanted to follow up on a previous comment and note that hCG was off label. One of the indications listed in the hCG label is selected cases of hypogonadotropic hypogonadism, in parentheses, hypogonadism secondary to a pituitary deficiency in male. But in terms of fertility, that's not included in the indications, but the hypogonadotropic hypogonadism is specified in that labeling. Thank you.

DR. VAIDA: Dr. McKinnon?

DR. McKINNON: We don't have anything. Thank you.

DR. VAIDA: Alright.

Although we're short on time, I'll just take one last question from Sandra Walker.

MS. FUSCO-WALKER: Yes. Thank you very much. It's Sandra Fusco-Walker. I just wanted to clarify one thing about the reporting.

The compounding companies who have registered as outsourcing facilities submit reports, but the rest of the compounding pharmacies in the country who have not registered do not

submit reports of what they're making; am I correct?

MS. COSEL: Yes, that is correct.

MS. FUSCO-WALKER: Thank you.

Committee Discussion and Vote

DR. VAIDA: Alright.

The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as public comments. We will proceed with the question to the committee, and I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Today's question is a voting question. Dr. Takyiah Stevenson will provide the instructions for the voting.

DR. STEVENSON: Question 1 is a voting question. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting

question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected.

Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote. You will have the opportunity to change your vote until the vote is announced as closed.

Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chairperson will

go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

Are there any questions about the voting process before we begin?

(No response.)

DR. STEVENSON: Alright. Seeing none, I will hand it back to the chair to read the question.

DR. VAIDA: Thank you.

The question before the committee, the 503A bulk drug substance list, enclomiphene citrate, FDA is proposing that enclomiphene citrate not be included on the 503A Bulks List. Should enclomiphene citrate be placed on the list?

Are there any wording questions that the committee has, questions about the wording?

(No response.)

DR. VAIDA: Alright.

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 subject to an applicable USP or NF monograph, or a component of an FDA-approved drug.

If there are no questions or comments concerning the wording of the question, we will now begin the voting on the question for enclomiphene citrate.

DR. STEVENSON: We will now move voting members to the voting breakout room to vote only. There will be no discussion in the voting breakout room.

(Voting.)

DR. STEVENSON: The voting has closed and is now complete. Once the vote results display, I will read the vote result into the record.

(Pause.)

DR. STEVENSON: The voting has closed and is now complete the vote results are displayed. I will read the vote totals into the record. The

chairperson will go down the list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

There are 4 yeses, 8 noes, zero abstentions.

DR. VAIDA: Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish. We'll start with the first person on the list.

Dr. Gupta?

(No response.)

DR. VAIDA: Dr. Gupta, is your microphone on?

DR. GUPTA: Hello. This is Dr. Anita Gupta. I voted yes.

DR. VAIDA: Okay.

Dr. Serumaga?

DR. SERUMAGA: Yes. Hello. This is Brian Serumaga from USP. I did vote yes on this one, and the reason is, as was stated in the FDA

presentation, USP does have a monograph for clomiphene citrate, which is the recipe [indiscernible], mixture, that contains one of the entities that is being considered today, which is enclomiphene citrate. They did provide enough evidence to show that the entity can be physically and chemically characterized, so for those reasons, I voted yes.

DR. VAIDA: Thank you.

Dr. Rebello?

DR. REBELLO: This is Elizabeth Rebello, and I voted no.

DR. VAIDA: Dr. Gura?

DR. GURA: Hi. Kathleen Gura. I voted no.

DR. VAIDA: Dr. Patel?

DR. PATEL: Hi. This is Kuldip Patel. I voted no based on lack of convincing efficacy evidence for the agreeable, appropriate clinical endpoints.

DR. VAIDA: Dr. McElhiney?

DR. McELHINEY: This is Linda McElhiney. I voted yes.

DR. VAIDA: Dr. Bui?

DR. BUI: I'm a non-voting member.

DR. VAIDA: Dr. Bogner?

DR. BOGNER: This is Robin Bogner. I voted yes.

DR. VAIDA: Dr. Dmochowski?

DR. DMOCHOWSKI: Roger Dmochowski. I voted no.

DR. VAIDA: Sandra Fusco-Walker?

MS. FUSCO-WALKER: This is Sandra Fusco-Walker. I voted no.

DR. VAIDA: Dr. Fensky?

DR. FENSKY: This is Tim Fensky. I voted yes.

DR. VAIDA: Dr. Lewis?

DR. V. LEWIS: Yes. This is Dr. Lewis. I voted no. I also think there's not very much evidence about clinical efficacy, absolutely none, and I would like to see a better -- or some study looking at clinical endpoints with the drug also. Also, in terms of alternative hCG, it may be on back order, but there's certainly clomiphene

citrate. So for those reasons I voted no.

DR. VAIDA: Thank you.

Allen Vaida. I voted no. I went along with the FDA's recommendation, and also had some questions on the thousands of prescriptions that Empower Pharmacy wrote, although the only good presentation was, I felt, from Dr. Masterson.

With that --

DR. STEVENSON: I'm so sorry, Dr. Vaida. This is Takyiah speaking. May I interrupt real quick?

DR. VAIDA: Yes.

DR. STEVENSON: Yes. Hi.

Dr. Anita Gupta, I do see on the screen that you voted no, but into the record you stated yes. Could you please verify your vote for the record?

DR. VAIDA: Oh, I'm sorry. I voted no.

DR. STEVENSON: So sorry. Dr. Anita Gupta.

DR. VAIDA: Oh.

DR. GUPTA: Yes. Dr. Anita Gupta voted no.

DR. STEVENSON: Thank you so much.

Continue, Dr. Vaida. Thank you.

DR. VAIDA: Alright. Thank you.

Although we're short on time, still I'd like to take a short break. It's 11:21, so if we could reconvene at 11:30, and we'll reconvene at that time.

(Whereupon, at 11:21 a.m., a recess was taken.)

DR. VAIDA: Alright. If we have everyone back from the break, we will now proceed with the FDA presentation on glutathione, and we'll hear from Dr. Emily Kneeream.

DR. STEVENSON: Hello, Dr. Vaida. This is Takyiah Stevenson speaking. I'm so sorry. Before we begin, we have one panel member to introduce that is joining us for the glutathione session.

Dr. Brian Green, could you please state your name and introduce yourself for introductions, please, and affiliation?

DR. B. GREEN: Yes. I am Dr. Brian Green from Hershey Medical Center. I'm sorry. Was there anything else I was meant to add for my introduction?

DR. STEVENSON: No, that is it. Thank you, Dr. Green.

DR. B. GREEN: Okay. Thanks for having me, guys.

DR. STEVENSON: And I'll hand it back to you, Dr. Vaida. Thank you.

DR. VAIDA: Alright. We can proceed now with Dr. Kneeream.

FDA Presentation – Emily Kneeream

DR. KNEEREAM: Good morning. My name is Emily Kneeream. I'm a clinical analyst with the Pharmacy Compounding Review Team in the Office of New Drugs, and I will be presenting glutathione. I would like to recognize the entire evaluation team, as well as the contributions of many other FDA colleagues who helped in this effort, and our special things to the Division of Dermatology and Dentistry and Division of Pulmonary, Allergy, and Critical Care in OND.

Glutathione was nominated for inclusion on the 503A Bulks List. The proposed dosage forms are oral; sublingual; topical; ophthalmic; nasal spray;

inhalation preparations; rectal; and injection. Glutathione was evaluated for 24 uses. These are listed in the slide.

This slide lists the criteria we consider when conducting evaluations for the 503A Bulks List. Glutathione is an endogenous tripeptide comprised of the amino acids cysteine, glutamic acid, and glycine. The bulk drug substance can be synthesized in well-developed protocols. Impurities are unlikely to be toxic. It is stable at room temperature as a solid or in a solid dosage form. As an aqueous solution, it is stable with proper formulation techniques, including protection from oxygen, pH buffering, and controlled storage temperature.

In conclusion, glutathione is well characterized, likely to be stable with protection from oxygen and controlled temperature and pH.

Glutathione is synthesized from precursor amino acids in nearly all cells of the human body, but the liver is the main source. It exists in two forms, oxidized and reduced. The reduced form is

the subject of this nomination. Its main function is as an antioxidant. It is an essential cofactor for numerous enzymes to inactivate various substances. It affects regulation of cellular differentiation, proliferation, and apoptosis. Disturbances in glutathione homeostasis may be associated with human diseases.

In rats, oral dosing showed increase in plasma concentration, peaking at 2 hours and lasting for 3 hours. Administration of the amino acid precursors of glutathione did not impact plasma glutathione levels. Inhibition of glutathione synthesis resulted in an increase in plasma levels through absorption of intact glutathione rather than its constituents. Via injection, it accumulated in the liver and spleen in mice and in the liver, spleen, and kidneys in rats.

Acute toxicity studies showed glutathione is tolerated when given by oral and parenteral routes at high doses for short periods of time. In a 26-week IV toxicity study in dogs, glutathione was

not associated with adverse effects on body weight or food consumption. No other data were captured from the study.

Genotoxicity data shows that it is not mutagenic in the absence of metabolic activation. In hamsters, it inhibited experimentally induced oral carcinogenesis. Insufficient nonclinical data exist to evaluate the toxicity profile of glutathione in reproductive or developmental toxicity studies.

Clinical pharmacokinetics of oral glutathione identified two studies. In one study in healthy volunteers, single doses up to 3 grams found a non-significant increase in plasma, suggesting negligible systemic availability.

A second study was oral glutathione 250 [milligrams], 1000 milligrams, or placebo for 6 months. Glutathione levels were measured at baseline and after 6 months. Levels in the 1000-milligram group were increased vs placebo in erythrocytes, plasma, lymphocytes, and buccal cells; whereas whole blood levels were increased in

the 250-milligram group. Levels returned to baseline following a 1-month washout period.

Authors concluded that the extent to which direct absorption may be responsible for the present findings is not known. Hydrolysis in the intestine is considered a primary obstacle for oral glutathione absorption.

Intravenous glutathione given in healthy volunteers showed a half-life between 10 and 15 minutes, and plasma levels returned to pre-dose values 30 minutes after dosing.

For clinical safety, we looked at FAERS reports and have broken down findings by route of administration. For IV route, reported AEs are two anaphylaxis with time to onset being from 30 minutes to 24 hours. Both patients discontinued. One was rechallenged and then experienced anaphylaxis. Another AE is hepatotoxicity with liver enzymes measuring 22 to 26 times normal. Infusion reactions and hypersensitivities were also noted. Both inhaled and oral routes reported hypersensitivity.

CAERS reports found 195 cases, and 194 of such cases involved multiple products, and the relationship to glutathione is confounded. One case listed glutathione as the sole ingredient and reported three skin-related AEs.

Clinical studies are also divided by route of administration. For IV, severe AEs, which warranted discontinuation, are deranged liver function tests and anaphylaxis. Other AEs are infusion site reactions; hair loss; GI disturbances; sleep difficulties; and dizziness. There are no studies on IV glutathione safety for chronic use.

For patients using IV glutathione for skin lightening, the switch from brown to red melanin production may increase the risk of sun-induced skin cancers in previously protected individuals.

For the oral and buccal route, AEs are nonspecific gastrointestinal. For the nasal inhalation route, AEs in the 600-milligram arm of a study, a patient withdrew due to tachycardia and cardiomyopathy, AEs resolved when glutathione

stopped; labored breathing, sore throat, and thirst. Oral inhalation route serious AEs include bronchoconstriction with severe wheezing, facial palsy, and hemoptysis.

Foreign regulatory authorities found the FDA of the Philippines warns against the use of IV glutathione for skin lightening and identified multiple AEs, including Steven Johnson syndrome; TEN, which may be serious and fatal; thyroid and kidney dysfunction; and severe abdominal pain. Thailand authorities also banned the use of IV glutathione for skin lightening for fear of severe adverse reactions, including anaphylaxis.

In conclusion, oral glutathione is minimally absorbed and appears to be associated primarily with local gastrointestinal AEs. IV glutathione has resulted in hepatotoxicity and life-threatening anaphylaxis, despite rapid elimination from the systemic circulation. Inhalation of glutathione identified significant safety concerns of bronchoconstriction. FDA has significant safety concerns, particularly IV and inhalation

formulations.

I will now discuss glutathione's effectiveness. FDA considered the available evidence of the substance's effectiveness or lack of effectiveness for a particular use, including reports in peer-reviewed medical literature. We evaluated 24 uses for glutathione. Please see FDA glutathione memo for our complete evaluation. Thirteen of these uses have clinical studies and will be discussed in the next slides.

First is on skin lightening. This refers to the use of depigmentation agents. Skin-lightening agents can be important tools in the management of disorders of hyperpigmentation such as melasma. The use of skin-lightening agents to lighten one's natural skin color is a global phenomenon, and a variety of substances have been used and been administered via topical, oral, or IV routes.

A study of oral buccal glutathione lozenge used for 8 weeks found a decrease in melanin indices. Authors recommended that a placebo-controlled randomized clinical trial with a

larger sample size and longer duration be undertaken.

An IV glutathione study in females using a visual assessment tool found the glutathione group showed a higher rate of skin lightening. This improvement was gradually lost after stopping treatment.

A review article on glutathione concluded there is little convincing evidence for glutathione as a therapy for hyperpigmentation. Efficacy remains questionable. The evidence of IV glutathione as a therapeutic modality for improving skin tone or pigmentation is minimum and contradictory. More evidence in the form of high-quality trials with better study design is vital.

In conclusion, a small IV glutathione clinical study appears to suggests it lightens the skin, but the effects seem to dissipate after discontinuation. Other studies failed to show a skin-lightening effect with glutathione or were inadequately designed. There are insufficient data

to support the effectiveness of oral glutathione for skin lightening. In addition, no data indicating any effect that glutathione may have to lighten the skin provides clinical benefit to address a disease or condition such as managing disorders of hyperpigmentation.

Next is on cystic fibrosis. One Cochrane review identified one trial comparing nebulized glutathione to saline, and found no evidence to recommend in CF, and that further research is required on improving outcomes. A second Cochrane review identified three studies. One was in oral glutathione, which found glutathione had positive effect on nutritional status and improvement in forced expiratory volume after 6 months treatment, however, imbalance of severe patients and a small sample size are potential biases.

In one study on inhaled glutathione, 3 of 4 endpoints were not different, however, peak flow improved in the glutathione group. Limitations of this study included unknown optimal dose and a small sample size. Another study on inhaled

glutathione, primary efficacy endpoints were not different between groups. A large number prematurely withdrew, 28 percent from the glutathione group and 42 percent from placebo.

More on cystic fibrosis; a trial of inhaled glutathione vs placebo for 12 months did not achieve measured outcomes in FEV1. A study of oral glutathione vs placebo found no differences between the groups in 6 months. The Cystic Fibrosis Foundation and Pulmonary Clinical Practice Guidelines Committee published a guideline on chronic medications for maintenance of lung health, which stated, "Evidence is insufficient to recommend for or against the chronic use of inhaled glutathione to improve lung function and quality of life."

In conclusion, the beneficial effect of glutathione is difficult to assess in patients with chronic conditions without a very large population sample and a long-term study period. There is insufficient information to support its effectiveness for the treatment of CF.

Next, asthma will be discussed. A 3-arm crossover study was identified in 12 patients with asthma, and they received a single dose of inhaled glutathione, SCG, or placebo. This was followed by a fog challenge. After fog challenge, the placebo group had a decreased FEV1 of 20 percent, and glutathione and SCG groups both decreased around 6 percent.

In conclusion, one single-dose small study in 12 patients provided insufficient information about population, exposure, or risk to support its use. Additional information provided on the effect that glutathione may have on the structure or function of the body does not provide evidence of any clinical benefit on the use of glutathione in asthma.

Next, I'll prevent oxidative stress, which is defined as a condition when the sum of free radicals in a cell exceeds the antioxidant capacity of the cell. A trial in healthy volunteers comparing oral glutathione to placebo found no change in the measures of oxidative stress. In a

study to evaluate prevention of contrast-induced nephropathy, or CIN, authors concluded glutathione may be a potential strategy against CIN, however, the most reliable markers of kidney damage were not evaluated.

In conclusion, scientific publications were not found that define a population, dose, or risk associated with glutathione for oxidative stress. Available data do not support the effectiveness of glutathione for oxidative stress.

Next is on reduction of side effects of chemotherapy. A trial to evaluate IV glutathione vs placebo in 185 patients undergoing chemo treatment did not reveal any evidence of benefit in any subgroup. Another study to evaluate IV glutathione vs placebo on prevention of neuropathy showed a lower incidence in the glutathione arm; and five small studies of various cancers with different chemotherapies, each lacking a control group that showed potential benefit in prevention or reduction.

In a study to evaluate the effect of

glutathione vs saline in colorectal cancer, although the glutathione group showed a reduction of neurotoxicity, they also showed a significantly lower level of the chemo agent. This is concerning as it may affect chemo's efficacy.

In summary, results of the studies for reduction of side effects of chemotherapy are mixed. Some show potential benefit, but they are small studies and lack a control arm. The largest placebo-controlled study showed no benefit of glutathione.

Regarding chemotherapy-induced peripheral neuropathy, or CIPN, the American Society of Clinical Oncology's Clinical Practice Guideline opines, "Due to a lack of high-quality, consistent evidence, no established agents are recommended for the prevention of CIPN," stating, "Specific agents, including glutathione, should not be offered for prevention of CIPN." The American Cancer Society states, "Study results are mixed and more research is needed."

In conclusion, available data are

insufficient to support the effectiveness of glutathione for reduction of side effects of chemotherapy. FDA concurs with health professional organizations that there is a lack of high-quality and consistent evidence to support the use of glutathione to prevent CIPN, and more research is needed.

Moving on to prevention of radiation injury, a study to decrease skin reactions caused by radiation in women undergoing radiation for breast cancer treatment received topical RayGel, which included glutathione or placebo. Skin reaction was lower in the glutathione group, but per authors, the substances that are absorbed could get into cancer cells and provide them with protection during radiation. This defeats the purpose of radiotherapy. Available data do not support the effectiveness to prevent radiation injury.

Next, I will discuss autism spectrum disorder or ASD. JHU CERSI identified one study in which children with autism spectrum disorder were randomized to receive either transdermal or oral

glutathione, however, the publication did not report efficacy outcomes. FDA did not identify any data to support the effectiveness in the treatment of ASD.

Next is on Parkinson's disease. A small study in 9 patients receiving IV glutathione showed decline of disability. Another IV glutathione vs placebo study of patients using the Unified Parkinson's Disease Rating Scale and motor skills produced no difference between the groups. A 3-arm intranasal glutathione in 2 doses or placebo study in patients resulted in mild clinical improvement in symptoms in both glutathione groups, but a follow-on phase 2B study receiving intranasal glutathione vs placebo resulted in neither treatment group being superior.

In conclusion, available data do not support the effectiveness for Parkinson's. Additional information on glutathione's use to affect the structure or function of the body does not provide evidence of clinical benefit.

HIV will now be discussed. A small study of

aerosolized glutathione did not show clinical efficacy. Another study of HIV infected individuals were given placebo or glutathione. Results for the glutathione group were an increase in some interleukin levels. A study noted that there is a significant decrease of glutathione levels in blood cells of HIV patients. Research has not yet shown glutathione is an effective treatment for HIV infection. While glutathione levels may be decreased in patients with HIV, no scientific literature was located that support its clinical efficacy in these patients.

Next is on otitis media. One trial of nasal aerosolized glutathione vs placebo on chronic otitis media in 60 children found that a 1-month follow-up noted improvement in two-thirds of the patients in the glutathione group. In conclusion, the minimum data indicating effectiveness for some study participants is insufficient to support effectiveness in treating otitis media.

Next is peripheral obstructive arterial disease. A trial of IV glutathione vs placebo on

walking-induced leg muscle pain relieved by rest showed the glutathione group had an increase in measuring blood flow in the leg after treadmill testing compared to rest measurements. In conclusion, the minimum data indicating effectiveness for some study participants is insufficient to support effectiveness in treating peripheral obstructive arterial disease.

Moving on to anemia, a small study of IV glutathione did not modify erythrocytes, platelets, or hemoglobin. Another uncontrolled study in dialysis patients saw improvement in red blood cells, hemoglobin, and reticular sites after IV glutathione was used to treat anemia.

A study of IV glutathione on the anemic status in patients with chronic renal failure showing anemia on hemodialysis received glutathione or placebo for 120 days. The glutathione group showed an increase in both hematocrit and hemoglobin on day 120 and a decline on days 150 and 180.

In conclusion, the minimal data indicating

effectiveness for some study participants is insufficient to support effectiveness in treating anemia.

Lastly is septic shock. Two 3-arm studies administering IV glutathione in patients with septic shock showed perioxidative stress and indirect markers of protection against oxygen-free radicals were improved. However, for both studies, it is unclear whether measured laboratory endpoints were appropriate to adequately determine glutathione's effect to change disease course. Thus, we conclude the minimum data indicating effectiveness for some study participants are insufficient to support its effectiveness.

For the remaining 11 of the 24 uses, please see FDA's memo for our evaluation of the available evidence of effectiveness, or lack of effectiveness, of drug products compounded with glutathione. As described in the memo, there is either no available information or insufficient evidence of effectiveness of glutathione in association with these nominated uses.

Here's what we found on the historical use of glutathione in compounding. JHU CERSI evaluated the use of glutathione in ASD. They found less than one percent of parents use glutathione injections for a child with ASD. Use of glutathione was rare and endorsed in less than 2 percent of responses in a sample of parents with children with autism.

Use of glutathione was less than 1 percent among children with and without autism in a sample of Medicaid claims from 2010 to 2014, and in phone interviews with some physicians and researchers little was known about glutathione, as it is rarely prescribed.

According to outsourcing facility reports, several facilities prepared single-ingredient drug products in a variety of dosage forms containing glutathione. They also reported preparing injection products containing glutathione and other drugs.

There have been published references to glutathione compounding since 2010, and the

International Journal of Pharmaceutical Compounding has published compounding formulations for several routes.

Glutathione is listed in the Japanese and European pharmacopoeias. Online promotion for compounding pharmacies and treatment clinics in the U.S. were found to promote use of glutathione in a wide variety of conditions and diseases. Use of IV glutathione for skin lightening is prevalent at medical spas across the country, offering glutathione injection and infusion skin-lightening treatments. In 2019, FDA issued a compounding risk alert for glutathione powder due to potentially high levels of endotoxins in the bulk drug substance and reported adverse events.

In conclusion, glutathione is promoted in the U.S. to treat a wide variety of conditions in various dosage forms. It is used in many regions around the world, and certain authorities have issued warnings against IV glutathione. It is rarely used to treat ASD.

Now, for our evaluation summary, glutathione

is well characterized and likely to be stable when compounded as solid or liquid products with proper formulation and storage conditions. Serious safety issues with glutathione use include anaphylaxis, hypersensitivities, hepatotoxicities, severe wheezing, and breathlessness. Glutathione injection and inhalation, in particular, raise safety concerns.

There is either no available information or insufficient evidence of effectiveness of glutathione with any of the proposed uses. Bioavailability of oral dosage form is minimal, and systemic exposure from injection formulation is associated with rapid metabolism. Approved drugs are available to treat several of the conditions that the glutathione is proposed to treat, many of which are serious or life-threatening, and available literature indicates that glutathione has been used since at least 1965, and compounding can be traced back to at least 2010.

After considering the information currently available, a balancing of the criteria weighs

against glutathione being added to the 503A Bulks List. Thank you very much. This concludes my presentation.

Clarifying Questions from the Committee

DR. VAIDA: Thank you.

We will now take clarifying questions for the FDA presenter. Please use the raise-hand icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it will be helpful to acknowledge the end of your question with a thank you, and any follow-up questions with, "That is all for my questions," so we can move on to the next panel member

The first question, Dr. Margolis?

DR. MARGOLIS: Yes. Hi. My name is David

Margolis. The question I had, I couldn't find any information in your presentation, nor in the package that we received, about whether or not it's ever been compounded topically for use in dermatologic conditions like post-inflammatory hyperpigmentation.

DR. KNEEREAM: Thank you for your question.

Can one of my colleagues in the OCQC potentially have this information? I'm not sure if that information is available to us.

DR. RUPP: Hi. This is Tracy Rupp with the Office of Compounding Quality and Compliance. We did find evidence of a compounding formulation published in the International Journal of Pharmaceutical Compounding for a transdermal cream. We also found information online on various websites and internet searches for transdermal products and topical products.

DR. MARGOLIS: Thank you.

Was there any information on successful treatment? I would assume it would be used for post-inflammatory hyperpigmentation in some of

those cases.

DR. RUPP: Thank you. I'll turn that question back regarding whether it's effective, and I'll turn that back to Emily.

DR. KNEEREAM: Thank you for your question. I'm not sure if Dr. Lewis in our Division of Dermatology would like to take this one, or I can refer back to our slides that we reviewed if you'd like.

DR. MARGOLIS: I didn't see anything in your slides. Was it there and I missed it? I apologize.

DR. F. LEWIS: This is Dr. Felisa Lewis in the Division of Dermatology and Dentistry. To my knowledge, there is no literature that exists about the efficacy of topical glutathione.

DR. MARGOLIS: Thank you.

DR. VAIDA: Thank you.

Dr. Calhoun?

DR. CALHOUN: Thank you. This is Bill Calhoun. I have a question regarding the adverse events, particularly the adverse events related to

the inhalational formulations.

The question turns on, really, what the population was in which those AEs were reported. You talked about bronchospasm, cough, and hemoptysis. So those would be common events to occur following inhalation of anything, even saline, in patients who have cystic fibrosis, or asthma, or COPD, et cetera, et cetera.

So the question for you, Dr. Kneeream, is whether it's the agency's position that it is the glutathione molecule per se that's responsible for bronchoconstriction, cough, and hemoptysis? Thanks.

DR. KNEEREAM: Thank you for your question. Let me go back to that slide for us.

I'm sorry. My slides aren't projected. Is there a way we can switch back to my slide deck?

DR. CALHOUN: It had been summarized on slide 39, I believe.

DR. KNEEREAM: We have them here, and we also talk about them earlier on. Let me find those slides for us.

(Pause.)

DR. KNEEREAM: This is our slide that we were referring to. In our clinical safety evaluation, we did identify four studies with safety assessments using the inhalation routes in a variety of patients.

DR. CALHOUN: So the question is actually pretty simple. Is it the position of the agency that the bronchoconstriction, severe wheezing, breathlessness, and hemoptysis are specifically causally related to the glutathione molecule, or are they a consequence of the population that was studied that might have had wheezing, cough, bronchospasm, and hemoptysis as part and parcel of the disease that was under study? Thanks.

DR. KNEEREAM: I appreciate your question. Unfortunately, we don't have the information to identify between patient concerns or drug-related concerns. It's just information that was provided to us in the literature. I don't think we can determine that. I don't know if Dr. Ganley would like to add any more information.

DR. GANLEY: Yes. Hi. I think, as you are well aware, it's very difficult to assess causality, even for approved drugs and when we're receiving adverse events. So I think in this context we're reporting this out as potentially related to it. It's just not a lot of data in the literature, and there's not a lot of exposure data where we could make an adequate assessment of that.

DR. CALHOUN: Alright. Thank you very much. That ends my question.

DR. VAIDA: Alright.

Dr. Evans?

DR. EVANS: Hi. This is Scott Evans. I have a question for the agency regarding our assessments of efficacy.

It's my understanding that, historically, the FDA has not emphasized changes in pulmonary function testing values alone as critical readouts in lung diseases, but that position seems to have moderated in recent years with the approval of certain antifibrotic agents based almost exclusively on effects on FVC. So when we look at

effects of glutathione, or the studies of glutathione, in cystic fibrosis, the agency's presentation indicates that there may be some effects, at least short-term, on FEV1 and maybe on peak flow as well.

So my question is, does the agency have any guidance regarding how to weigh pulmonary function testing and effects in the absence of clear indications of functional or survival changes? Thank you.

DR. KNEEREAM: Thank you very much for your question. I'm not sure if Dr. Lan from pulmonary would like to address this.

DR. LAN: Hi. This is Jennifer Lan from the Division of Pulmonology, Allergy, and Critical Care.

Can you repeat the last part of your question, sir? Thank you.

DR. EVANS: Certainly. The last part of my question was, when considering efficacy of this agent, does the agency offer any guidance on how to weigh pulmonary function values alone in the

absence of any evidence of functional or survival advantages?

DR. LAN: I --

DR. PATERNITI: Hi. This is Miya Paterniti -- oh, go ahead, sorry -- from the Division of Pulmonology, Allergy and Critical Care. Generally speaking, I think you touch on an important point, which is that we do consider lung function as part of an overall effectiveness assessment.

So on its own, especially given the issues with the trial design and other bias that may have occurred, we weigh the totality of all of those considerations in terms of how we weigh pulmonary function alone. There have been situations where we have approved drug based on pulmonary function alone, but this is indication-specific and, again, is considered within the totality of the effectiveness information.

DR. EVANS: Okay. Thank you.

DR. VAIDA: Dr. Bui?

(No response.)

DR. VAIDA: Dr. Bui, do you have a question?

DR. BUI: Yes. This is Dr. Bui here, and a clarification for the agency.

You mentioned that in slide 16, the Philippines and Thai health authorities had some concern about IV glutathione, and in slide 38, you mentioned that certain authorities have issued a warning against IV. I'm just wondering, besides those two health authorities, what other health authorities have concern about IV glutathione, and if they have specific concerns about certain conditions.

DR. KNEEREAM: Thank you for your question.

DR. RUPP: Hi. This is --

DR. KNEEREAM: Oh, go ahead. Sorry, Tracy.

DR. RUPP: Thank you, Emily. I can take this.

This is Tracy Rupp with the Office of Compounding Quality and Compliance. Regarding your question about health authorities in other countries, we're also aware that authorities in the Philippines, Asawanonda had issued warnings against

the use of IV glutathione for skin lightening, citing lack of safety and efficacy data, and some concerns regarding side effects.

There's a link in the evaluation with more information about those warnings that have been issued. Then, Emily also mentioned the compounding risk alerts that FDA issued for -- it was related to the use of high levels of endotoxins related to the use of glutathione powder that contained potentially high levels of endotoxins leading to AEs. Then you already mentioned the Thailand issue with banning IV glutathione because of adverse reactions, including anaphylaxis. Those are those are some of the ones that we are aware of currently.

DR. BUI: So nothing from Europe or Japan health authorities having concern about IV glutathione?

DR. RUPP: I don't think we're aware of information from Japan at this point, but if any of my colleagues would like to add, feel free to do so.

(No response.)

DR. RUPP: Did we answer your question or did you have any additional questions?

DR. BUI: I was just waiting for your follow-up. I'm not sure you have an answer regarding Japan, but it sounds like -- or Europe. It sounds like you don't have an answer for that.

DR. RUPP: If there are any warnings?

DR. BUI: Yes, in Japan or Europe.

DR. RUPP: I'm not aware of warnings in the EU or in Japan. If any of my colleagues would like to add any additional information about anything that they're aware of, feel free to do so. But I'm hearing that they're not aware of other warnings in EU or Japan as well.

DR. BUI: Okay. Thank you. I have no follow-up questions.

DR. VAIDA: Thank you.

Dr. Margolis, did you have a follow-up question?

DR. MARGOLIS: I did not, and I realize I didn't take my hand down. I apologize.

DR. VAIDA: Okay.

Ann Taylor from the FDA, did you have a comment or question?

DR. TAYLOR: Yes, sir. Dr. Ganley would like to be recognized for a comment.

DR. GANLEY: Yes. This is Charley Ganley from FDA. Just in reference to the previous questions on cystic fibrosis patients, I think one of the reasons that we had a discussion today for INDs is not just for this ingredient but for some of the other ingredients as to whether certain populations who have serious diseases should be evaluated under INDs as opposed to putting glutathione on a 503A list and permitting the treatment of patients with a variety of diseases, as evidenced from the vast list that we reviewed in the list that's available online to which it's being marketed, and whether some of these patients should be evaluated under INDs, either under expanded access or under a regular IND, because of the lack or paucity of data that supports its effectiveness. That's all I had to say. Thanks.

DR. VAIDA: Thank you.

We will now proceed with the nominator presentation. We have one presentation from Dr. A.J. Day, who's speaking on behalf of the Professional Compounding Centers of America and National Community Pharmacists Association.

Dr. Day?

Nominator Presentation – A.J. Day

DR. DAY: Good day, ladies and gentlemen. Thank you for the privilege of speaking to you today. We have a lot of material to discuss and very limited time, so let's jump right into it. My name is A.J. Day, vice president of Clinical Services with PCCA. My presentation today is on behalf of PCCA, Professional Compounding Centers of America, and NCPA, the National Community Pharmacists Association.

Page 4 of FDA's evaluation shows that the agency does not have concerns over the stability of compounded glutathione in solid, semi-solid, or liquid dosage forms, including injections. From a formulations perspective, the stability evaluation

would apply to sterile solutions, which includes inhalations.

Page 5 identifies likely impurities from the manufacturing process and states plainly that, "The impurities mentioned above are unlikely to be present at a highly toxic level." No concerns were raised about the particle size or polymorphisms.

Moving to the safety evaluation, glutathione is an endogenous peptide which is well understood. FDA's evaluation states, "Available acute toxicity studies in animals show that high levels of glutathione are tolerated. Glutathione is not mutagenic in the absence of metabolic activation."

Page 24 of FDA's analysis states that, "IV glutathione has resulted in hepatotoxicity and life-threatening anaphylaxis." In fact, hepatotoxicity is only cited by FDA in the literature in a single case study, which was a letter to the editor and does not show causality for glutathione. Anaphylaxis is not cited in any clinical trials.

The letter to the editor in the Japanese

case study states, quote, "He was anxious concerning disease progression and consulted another private clinic that he found on an internet service, from which he received intravenous GSH, 1200 milligram daily injection per week."

No information is provided about the quality, stability, and source of the glutathione use. The patient was on three other Parkinson's medications and nine additional concomitant medications. DLST was equivocally positive for glutathione, meaning it is uncertain. FDA specifically states, "False positives and false negatives results may occur from this test."

The first report of anaphylaxis is in a latex-sensitive patient. No details are provided as to the patient's exposure to latex or latex derivatives. The patient also experienced anaphylaxis to ceftriaxone a day later. The source and dose of glutathione are unknown. Based on the limited information available, we cannot conclude that glutathione was the cause of the issues this patient experienced.

The second report of anaphylaxis that FDA sites is a cancer patient in China who developed pharyngeal edema, cyanosis, and airway whistling during his first infusion of glutathione. The patient was started on oral capecitabine the same day. Timing related to anaphylaxis event is unclear. This patient's other health conditions and medications are not discussed. Known adverse events for oral capecitabine include dyspnea, pharyngeal disorder, and respiratory distress. Again, based on the limited information, we cannot conclude that glutathione was the cause of the issues this patient experienced.

In that same paragraph on page 24 of their evaluation, FDA points to the Marrades study from 1997, planting significant safety concern for inhaled glutathione for patients with asthma. This trial enrolled 8 patients. The study was conducted in Barcelona, Spain, and the glutathione was provided by a physician's office in New York in vials. No identity or potency testing was conducted on the glutathione use. pH was checked

and reported to be 3.0.

The authors provide plausible explanations for the bronchoconstriction their patients experienced. As reduced glutathione is oxidized, it releases sulfites. Several studies have shown that patients with asthma are, quote, "exquisitely sensitive to the bronchomotor effects of sulfites, concentrations below 1 part per million. The finding that all patients tested showed a significant bronchoconstrictive response to metabisulfite challenge, correlated inversely with the threshold of responsiveness to GSH, lends further support to the mechanism of bronchoconstriction induced by sulfite formation."

As previously stated, the glutathione used in this trial was shipped from a physician's office, and no information is known about the original source or how it was prepared and stored. The pH of 3.0 would lead to increased oxidation of the formulation, accelerating the production of sulfites, which may increase the issues observed in these patients.

As FDA's own stability evaluation states, "pH protection from oxygen and proper formulation techniques are important for the stability of this compound." We do not know the details of formulation used, though it is highly likely that the pH of their formulation led to an increase in oxidized glutathione, which creates disulfides, and asthma patients are known to be sensitive to these molecules. FDA's stability evaluation identified a pH of 6.4 in refrigerated temperature, yielding a shelf life of 112 days for reduced glutathione.

Other clinicians have evaluated this same data from this Marrades study, which was, again, limited to 8 patients, and have come to much less alarming conclusions than FDA. While acknowledging that bronchoconstriction in asthmatic patients is worrisome and potentially life-threatening, Prousky's 2008 review article -- which evaluated 11 studies which met the inclusion criteria, including 159 patients -- states that, quote, "GSH inhalation is very safe."

Specifically about the Marrades study, he

states, quote, "If proper precaution such as sulfite testing are done prior to testing, this serious side effect should be avoidable."

I would add that the pH of the formulation should be considered along with the qualitative attributes of starting material and appropriate end-product testing, such as sterility and endotoxins.

Additional data from Borok and colleagues was not evaluated by FDA, despite being provided in other nominating materials. Twenty-nine patients were enrolled, and researchers stated, quote, "Detailed safety evaluations were done throughout the study," end quote. Authors conclude that aerosol therapy of IPF with glutathione is safe. Unfortunately, more details about the specific safety measures are not available. This was published as a, quote, "short report."

In the review of glutathione for HIV, FDA evaluated this study by Holroyd and colleagues. This study does provide details for the safety evaluation of inhaled aerosolized glutathione.

Quote, "To evaluate possible toxicity of the glutathione aerosol, symptoms, physical examination, routine blood studies, chest radiographs, electrocardiogram, renal function, arterial blood gases, and test of pulmonary function were followed carefully throughout the study. In addition, visual examination of the respiratory mucosa and analysis of differential cell count in bronchoalveolar lavage fluids were performed before the first and after the last aerosol doses."

They obtained purified glutathione powder and addressed potency, sterility, and pyrogens. The authors state that, quote, "No symptoms referable to the aerosol administration of glutathione were noted, and the physical examination and all clinical measurements remain stable following treatment with glutathione."

Most recently, a meta-analysis by Wang and colleagues was published in 2021. While focused on Parkinson's disease, the review of 450 patients through 7 randomized-controlled trials concludes

that, quote, "The pooled results of these studies revealed that the therapeutic dose of GSH is safe. Further patient studies also indicate that when GSH was repeatedly administered at doses of up to 5 grams per day, both orally or IV, no toxicity was observed."

We have ample evidence to show that inhaled, injected, and oral glutathione is safe. Let us now shift our focus to the efficacy evaluation for glutathione and cystic fibrosis.

FDA evaluated the study by Clark Bishop and colleagues from 2005. This is a randomized, double-blind, placebo-controlled, parallel-designed clinical trial. A quick note, that I contacted Dr. Bishop to discuss his research and invited him to speak at this meeting. He was out of the country for a few days. Other researchers were also contacted, and all were unable to clear their schedules on such short notice.

If FDA would give us more than 5 business days to review the briefing packet before speaker names are due, they may receive more valuable

stakeholder engagement. This is a consistent issue with these PCAC meetings.

Bishop and colleagues report that small airway functions improved in the GSH group with, quote, "significant improvement in peak flows and the tendency toward significance of the FEF 25 to 75 in ancillary compliance analysis." Because 2 subjects in the GSH group did not record peak flow data, the peak flow comparison is comparable to the compliance analysis.

They go on to state, "While the effect size in peak flow analysis is relatively small, improvement in small airway function is noteworthy because research in CF pathophysiology suggests that the changes in peripheral airflow proceed changes in FEV1 and FVC in this disease." Subjective sense of improvement and subjective assessment of cost frequency are secondary indicators, which also had significant improvement in this study. None of the outcomes significantly favored the control group over the GSH group.

Also in 2005, Dr. Bryan Day published an

evaluation of literature on glutathione for cystic fibrosis. Dr. Day notes the small size of the Bishop trial and states, "The results are encouraging." In describing the results of studies by Roum, Griese, and Bishop, Dr. Day states, quote, "Inhaled glutathione was well tolerated and efficacious in improving a variety of clinical indicators in all three studies reported."

With three small clinical trials with positive findings now published, it seems clear that the next logical step is a large multicentered clinical trial. Several obstacles remain to be overcome. These include the cost of safety studies, agreement on dosages, primary indicators, and support from the pharmaceutical industry for an orphan indication.

Bishop had another study published in 2013 with 44 patients, and FDA notes the conclusion that oral glutathione should be considered in pediatric cystic fibrosis patients. Another 2013 study by Griese enrolled 153 cystic fibrosis patients. Primary efficacy endpoints were not different

between the two groups in this study. This is the only clinical trial cited which does not show benefit from the glutathione therapy.

This trial was plagued by patient withdrawal, including 29 percent of the GSH group in interest only, and 42 percent of the placebo group, suggesting not a failure of the GSH therapy but other issues with the protocol.

As noted in FDA's evaluation, the 2013 cystic fibrosis pulmonary guidelines do not recommend for or against the chronic use of inhaled glutathione. The group making these guidelines only evaluated one study on GSH specifically. The other study cited in this part of the guidelines use acetylcysteine, not glutathione.

FDA's evaluation of the 2015 study by Calabrese and colleagues notes the author's comment that "most enrolled children had a normal spirometry at baseline with no room for improvement." Looking at that study, researchers confirmed a significant decrease in FEV1 in the adult placebo group that did not occur in the

glutathione group. A decline of functional parameters in the placebo group, although not statistically significant, was also observed by Griese.

Back to the acknowledgement of no room for the children enrolled, when the researchers mixed the results of adults and children sharing an FEV1 below 81 percent, they confirmed a significant improvement of the FEV1 in the glutathione arm compared to the placebo. Nevertheless, pediatric patients that assumed glutathione showed a significant improvement of the distance walked in 6 minutes that is considered a marker of disease severity, according to previous data.

Quote, "Based on the result of this clinical trial, the treatment with inhaled glutathione is assumed to lead to an almost immediate improvement in FEV1 in patients with moderate lung disease, a stabilization of BMI in adult population, and an improvement of the 6-minute walking test in children." This data was not evaluated in the 2013 guideline statement previously discussed, which,

again, did not take a position against inhaled glutathione.

FDA's evaluation of the 2015 study by Visca identified the various parameters in which glutathione was of benefit to patients. Again, this data was not evaluated for the previously stated 2013 guidelines. Per the authors, patients in the GSH group showed significantly improved results on a repeated measure analysis of variance compared with the placebo group on all four primary outcome measures.

No adverse events were noted in this study, except for one single adverse event in the placebo group. This is further evidence of the safety of oral glutathione. Dosing was weight-based, which also underscores the need for compounding. No patient in the GSH group worsened on any of the 11 subjective measures of GI symptoms during the course of the 6-month trial, and there was a statistically significant trend towards the improvement in symptoms in the GSH group over time compared with the placebo group, except for nausea,

heartburn, and fewer than 2 bowel movements per week.

FDA acknowledges the severity of cystic fibrosis and states that there are many approved therapies for the treatment of CF, which weigh against inclusion of glutathione on the 503A Bulks List. Let's take a quick look at the items the FDA lists in this section.

The various anti-infective agents are indicated for infections associated with CF, not to treat CF. Dornase alfa and sodium chloride are to thin the mucus, not to treat CF. Albuterol and levalbuterol are to treat coughing and shortness of breath in patients with CF; they do not treat CF. There are FDA-approved products to treat CF. Ivacaftor, or monotherapy, or in fixed combinations with one or two other agents, is on the market and available under brand names only.

According to these reports, which include FEC pricing data, the cost for these medications ranges from $311,503 per patient/per year for this first one, or $23,896 per 28-day pack, to $300,000

and $259,000 per patient/per year for these two on the right of your screen.

These wildly expensive FDA-approved treatment options have limited benefit and limited patient populations to serve. Again, according to the same articles, patient benefit was seen as 3 percent improved lung function for Orkambi to 14 percent improved lung function for Trikafta. The manufacturer cited that only 2,600 patients globally had the specific genetic mutation that made them eligible for Kalydeco's first approved indication. The manufacturer for these drugs also has another similarly priced combination drug.

These drugs also carry significant risks. Adverse events from these drugs include neurologic adverse events; respiratory infections; conjunctivitis; elevated LFTs; liver injury; elevated bilirubin; GI events; various rashes and dermatologic events; increased blood creatine phosphokinase more than 5 times the upper limit of normal; increased blood pressure; and many others.

FDA states that the beneficial effects of

glutathione are very difficult to assess in patients with chronic infection without very large population samples and a long term, at least 6 months, study period. This brings us back to the article from Dr. Bryan Day, where he identifies several obstacles to larger studies for glutathione, including the cost of studies and support from the pharmaceutical industry.

Glutathione is a natural endogenous molecule available through compounding for at least 32 years. These factors make it very unattractive for pharmaceutical companies generally. Even when they have the prospect of patents and market exclusivity, pharmaceutical companies identify such small patient populations, that they feel they must charge $300,000 per patient/per year for their product.

Another issue with FDA's statement about very large population samples and long-term study periods is raised by the advisory.com article. They state that the branded product Trikafta was shown to be effective in two clinical trials. The

first was a 24-week trial in 403 patients; the second was a 4-week trial in 107 patients. Those are for novel molecules seeking FDA approval. We are talking about a well-known, endogenous molecule that has been around for over 30 years.

To wrap up our discussion on glutathione for cystic fibrosis, the overwhelming majority of data suggest that inhaled IV and oral glutathione is safe at doses up to 600 milligrams per day or 65 milligrams/per kilogram per day. Efficacy data supports glutathione as an option for patients with cystic fibrosis. It suggest positive subjective outcomes. The majority of studies show positive objective outcomes. No studies show inferiority to placebo. No studies report serious adverse events in treatment groups.

This chart summarizes the clinical trials for cystic fibrosis I've presented here: seven trials, five of them placebo-controlled, double-blind, and randomized. None of the trials identified significant safety signals in the glutathione arm. Here are the references for the

cystic fibrosis clinical efficacy discussion.

Now let's discuss glutathione in reducing side effects of chemotherapy. FDA mentioned the 2014 ASCO practice guidelines and that they don't recommend glutathione for the prevention of CIPN. Reading the ASCO guidelines, they state that six small randomized trials evaluated the protective effects of GSH against platinum-based neurotoxicity. Five of these trials reported a statistically significant reduction in neurotoxicity in one form or another with administration of GSH compared to placebo. Benefits included reduction in incidence and severity of neuropathy and improvements in nerve conduction and quality of life.

They then point to a single trial with a different chemotherapeutic regimen which did not prove efficacy of GSH in the prevention of CIPN, and conclude that they do not recommend using glutathione for CIPN. While the results of this one study suggest that glutathione may not be an effective agent for carboplatin-induced CIPN, these

results may not be applicable for cisplatin- or oxaliplatin-induced neurotoxicity.

Let's take a quick look at some of these studies. Cozzaglio and colleagues enrolled 11 patients, 10 of whom were evaluable at the end of the study. The study was designed to evaluate the use of high-dose cisplatin with 5-fluorouracil, utilizing glutathione to protect patients from neurotoxicity associated with high doses of cisplatin. The authors concluded that the lack of incidence of severe neurotoxicity supports the role of reduced glutathione as a potential protective agent against cisplatin toxicity.

My slide did not advance for that; my apologies.

A study by Di Re and colleagues enrolled 79 patients with up to 5 courses of high-dose cisplatin. While peripheral neurotoxicity and ototoxicity were the most significant long-term toxicities, as FDA states, the researchers also state that the severity of these side effects were apparently less than has been reported with other

high-dose cisplatin regimens.

They state, quote, "The efficacy and tolerability of the regimen confirmed the feasibility of this new approach for including glutathione in order to increase cisplatin dose intensity." The researchers state that the value of patients tolerating these doses with the aid of glutathione, quote, "the main advantage of the high-dose cisplatin regimen with GSH is that the dosage of 160 milligrams per meter squared, per course, can be maintained for 5 cycles of treatment, thus allowing the 100 percent delivery of planned doses in most patients."

A study of 50 patients by Bohm and colleagues --

DR. VAIDA: Dr. Day?

DR. DAY: Yes?

DR. VAIDA: Dr. Day, we are running on time here. If you could try to wrap it up so we'll be able to take some clarifying questions, please.

DR. DAY: I will move as quickly as possible.

A study of 50 patients by Bohm and colleagues shows that toxicity was moderate when using glutathione protection with the lack of significant nephrotoxicity. Neurotoxicity and ototoxicity were acceptable, and in no patient was treatment discontinued for these side effects. They say, quote, "The impressive efficacy suggests a possible contribution of reduced glutathione itself in improving the outcome as reported by preclinical studies."

FDA and ASCO mentioned the Leal study and the failure for glutathione to provide benefits in CIPN. The authors themselves have a different perspective on the results. This trial enrolled 185 patients. There were no significant differences on cancer outcome, indicating that glutathione does not interfere with the chemotherapy, and additionally, no statistically significant or clinically apparent toxicity differences between the glutathione and control arms with regard to multiple evaluated toxicities.

Note that this Leal study was the first

trial involving carboplatin with glutathione. The authors state that while the results of this study support that glutathione is not an effective agent in the prevention of taxane-induced CIPN when given in combination with carboplatin, the current results may not be applicable for cisplatin- or oxaliplatin-induced neurotoxicity.

They also cite other research with therapies where chemo-induced neuropathy may be different for different chemotherapeutic agents. They state this may explain the differences between the findings from the present study and what has previously been suggested in other trials looking at oxaliplatin- or cisplatin-based therapies.

Reviewing more literature, FDA states that Bohm's 1991 publication showed that treatment was well tolerated with no nephrotoxic or neurotoxic events with the regimen of cisplatin and cyclophosphamide. Gebbia and colleagues showed in 1992 that cisplatin and 5FU plus folinic acid and glutathione showed that glutathione appeared to be able to reduce, at least partially,

cisplatin-related nephrotoxicity, thus delivering higher cisplatin doses.

In 1995, Cascinu showed that in a 15-week, 50-patient, double-blind, placebo-controlled randomized trial, no patient showed clinically evident neuropathy in the glutathione arm; 16 patients in the placebo arm did. After 15 weeks, 4 of the 24 assessable patients in the glutathione arm suffered from neurotoxicity versus 16 of 18 in the placebo arm; P, a value of 0.0001. The chemotherapy response rate was 76 percent in the glutathione arm; 20 percent complete response versus 52 percent in the placebo arm; and 12 percent complete response.

In a follow-up study in '97, Cascinu showed that with 105 patients on cisplatin-based therapy, only 3 subjects complained of neurotoxicity, one of WHO grade 1; two of WHO grade 2. Soon after, Boehm's 1999 trial showed that 50 patients on IV glutathione with cisplatin therapy had acceptable neurotoxicity and ototoxicity, and no patient discontinued treatment due to toxicity.

In 2002, Cascinu and colleagues published another study, this time utilizing glutathione or placebo with oxaliplatin in 52 patients. At the fourth cycle of treatment, 7 patients showed clinically evident neuropathy in the glutathione arm, whereas 11 patients in the placebo arm did. After the eighth cycle, those numbers were 9 of 21 assessable patients in the glutathione arm versus 15 of 19 in the placebo arm.

A neurophysiologic investigation showed a statistically significant reduction of the values in the placebo arm, but not the glutathione arm, showing patients were better off with glutathione in this trial. The response rates of the chemotherapy was 26.9 percent glutathione, 23 percent in the placebo arm, showing no reduction in activity of oxaliplatin with glutathione utilization.

On page 39 of their glutathione evaluation, FDA states that the Milla study showed statistically significant reduction in neurotoxicity in the glutathione arm compared to

the placebo warm. However, the lower total area under the plasma concentration time curve in the glutathione arm was lower than in the placebo arm.

FDA goes on to conclude that one study showed that glutathione significantly lowered the level of a chemotherapeutic agent, which may affect efficacy. To be clear, the authors addressed the implications of this measurement directly. Even the abstract states that the platinum DNA adduct formation shows no statistically significant differences between the glutathione and placebo arms.

This study indicates that co-administration of glutathione is an effective strategy to reduce the oxaliplatin-induced neurotoxicity without impairing neither the pharmacokinetics of oxaliplatin, nor the platinum DNA adduct formation. This study was designed --

DR. VAIDA: Dr. Day --

DR. DAY: -- to study pharmacokinetics.

DR. VAIDA: -- could you please wrap it up so we could get some questions, and also have the

open public hearing, please?

DR. DAY: Certainly, Dr. Vaida. There's an abundance of data and clinical trials that were presented, and I'm simply trying to respond to those.

Can you give me a specific amount of time that you would like me to wrap up in?

DR. VAIDA: Yes, like three minutes.

DR. DAY: Three minutes; noted.

This study was designed to study pharmacokinetics. The authors also do not consider the area under the concentration time curve to be a, quote, "main pharmacokinetic parameter." The authors offer a more in-depth discussion on this point in the full article, even showing that there is no glutathione influence on platinum DNA adduct formation in tumor cells as well. Quote, "The ability of GSH to prevent the oxaliplatin-induced neurotoxicity without impairing platinum DNA adduct formation in tumor cells, or in white blood cells taken as a model, could be explained by the pharmacokinetics of this model."

Quote, "The lack of toxicity and interference of pharmacokinetics and effects of oxaliplatin suggest that GSH may be a promising drug for the prevention or delay of oxaliplatin-induced neuropathy in colorectal cancer patients."

Now, FDA acknowledges the severity of the side effects of chemotherapy. They go on to state that there are alternative drugs with FDA approval to reduce the side effects of chemotherapy, including palifermin injection, amifostine, dexrazoxane, and mesna. They conclude by saying that the existence of approved drugs to treat the disease weigh against the addition of including glutathione on the list, particularly in light of adverse events.

As previously shown in these slides, glutathione is safe. Looking specifically at the list of approved products FDA cites, palifermin is not approved for neuropathy; it is approved for mucositis. Dexrazoxane, mesna, and amifostine are not indicated for neuropathy. They have

alternative indications, indicated on this slide. Even the 2014 article by Leal and colleagues states that there is, quote, "no recommended agents for preventing chemo-induced neuropathy."

It is important to note that glutathione injection is approved by the Italian Medicines Agency for the prevention of neuropathy from cisplatin and related analogs. At the recommended doses, glutathione injection does not interfere with therapeutic activity of the chemotherapeutic agent. This product information was obtained in Italian and then translated to English. Copies of the original and translated material were sent to the FDA along with my slides. I had requested that they be sent to the committee as well.

The Italian labeling also addresses use in pregnancy and lactation. They also address the side effects, which are consistent with the data presented here, stating that they are generally mild and infrequent with a likelihood of injection site reactions. The dosing guidelines are also consistent with the data presented here.

I've presented here 932 patients evaluated in 15 published trials from 1994. Only one study failed to show GSH benefits, using a different chemo regimen from all other studies. The authors note zero safety issues, no interference with the chemo regimen, and provide a plausible hypothesis for the unexpected results; 15 trials showing no clinically meaningful interaction with chemotherapy or clinically meaningful patient safety concerns. It is an approved product in Italy for CIPN. There are zero FDA-approved products for this serious condition, and removing glutathione as an option for patients does nothing to serve public health. It harms public health.

I have occupied the three minutes that Dr. Vaida had granted me, though I do have further slides and data to present. In the interest of time, I will defer to the committee.

Clarifying Questions from the Committee

DR. VAIDA: Okay. Thank you, Dr. Day.

We will now take clarifying questions for the nominator presenter. Please use the raise-hand

icon to indicate that you have a question, and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can. If you wish for a specific slide to be displayed, please let us know the slide number, if possible.

Finally, it will be helpful to acknowledge the end of your question with a thank you and end of your follow-up question with, "That is all for my questions," so we can move on to the next panel member.

Dr. Lewis?

DR. F. LEWIS: Yes. This is Dr. Felisa Lewis, a dermatologist in the Division of Dermatology and Dentistry. I did want to make a few clarifying comments.

First, I wanted to correct my earlier statements in response to Dr. Margolis' question about topical glutathione in the literature. I had said that there was no literature, but in fact

there are very few articles about the topical use of glutathione, and none of them were specifically for the purpose of treating a medical condition such as melasma. They were primarily for photo aging or for skin lightening.

I did want to emphasize that while there are some of those recognized medical treatments that have localized hyperpigmentation such as melasma, glutathione is not a typical substance that is used for compounding in topical products. Instead, glutathione has been more widely used globally, and its IV formulation is for overall skin lightening -- [inaudible - feedback].

Can you hear me? Because I'm getting some feedback.

(Pause.)

DR. F. LEWIS: Okay. I think the feedback is gone. Sorry.

To continue -- this is Dr. Lewis again -- I believe I was saying that glutathione has been more widely used globally and as IV formulation for overall skin lightening. I wanted to emphasize

that there is no recognized medical condition where the first-line treatment is overall skin hypopigmentation or depigmentation.

Besides the immediate potential for systemic adverse reactions, we should also consider the long-term implications of changing a person's overall skin tone because any reported degree of skin lightening achieved is temporary, and the maintenance of this hypopigmentation would require the regular and chronic administration of IV glutathione.

While the purpose of this advisory committee is to weigh the scientific evidence of the use of glutathione, we should not ignore that the desire for overall skin lightening is driven by cultural standards that are deeply rooted in some ethnicities of skin of color, i.e., Fitzpatrick's skin types 3 through 6 such as in Asia and Africa, where the fairness of one's skin tone is equated with higher social status and beauty.

So despite the widespread messages of diversity acceptance that are currently prevalent

in the United States, these cultural stereotypes and beliefs persist in U.S. populations of these ethnic groups, and for this reason, there is also a body of literature authored by prominent board certified dermatologists that speak unequivocally against the use of glutathione for skin lightening. Thank you.

Open Public Hearing

DR. VAIDA: Alright.

If there are no questions for Dr. Day, we will move on to our open public hearing session.

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

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

have with the product and if known, its direct competitors.

For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting. Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any financial relationships. If you chose 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 on 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.

Speaker number 1, your audio is connected now. Will speaker number 1 begin and introduce yourself? Please state your name and any organization you are representing for the record.

DR. ANDERSON: Hello. My name is Dr. Paul Anderson from Seattle Washington. I have no financial relationships to disclose in regard to this meeting or this topic.

I am formerly one who testified on behalf of nominations by AANP, and today I'm just giving clinical background for the use of glutathione. I am a physician and researcher in Seattle, Washington, and was formerly the director of interventional medicine in a five-year NIH-funded oncology trial in collaboration with the University of Washington Seattle Cancer Care Alliance, Seattle Children's Hospital, and Bastyr University.

In this trial, in addition to in my private

practice, we used a great deal of compounded glutathione in the integrative oncology center. In addition, I'm a co-author of the textbook, A Scientific Reference for Intravenous Nutrition Therapy, from CAO Medical Publishing, and the focus of my practice and research is oncology patients, supporting them through standard of care and mitigating side effects after standard of care.

We have used glutathione in a compounded form as a modality for 20 years-plus at this point. The scope of the glutathione use of my clinics that I was supervising over those 20 years, I estimate that I've ordered and monitored over 20,000 doses of compounded glutathione. Those doses were intravenous, as well as respiratory administration.

In relationship to the NIH trial, we used glutathione in a number of settings. One was in referral from the University of Washington Radiation Oncology Center, after radiation therapy was completed, to assist patients in nerve repair due to radiation nerve injury. Other uses were for general quality of life and also co-administration

with platinum drugs to decrease CIPN, as both of the prior presenters have already talked about.

I do want to point out that I would agree with Dr. Day regarding his interpretation of the glutathione and oncology data that he had a chance to present, part of anyway. In our trials and in looking at all of these doses administered anecdotally, I would also affirm that we not only have efficacy in the oncology uses, but also a great margin of safety. The people and indications that we primarily used were, as I mentioned, post-treatment recovery, nerve damage, CIPN, acute and chronic respiratory conditions, and other activities of daily living, quality-of-life issues.

Retrospectively -- and this is anecdotally, not published anywhere, but in those 20,000-plus doses, we've had no grade 3, 4, or 5 adverse events. Grade 2 is estimated at under 20 total in the 20,000, and grade 1 adverse events are estimated under 100 in that 20,000 dose range, and this is using the standard adverse event grading by a cancer therapy evaluation program.

In closing, thank you for your time, committee, and in the nearly 20-year span, we've been able to clinically use compounded glutathione. I and colleagues have found it to be incredibly safe and effective therapy in support of patients with cancer and other chronic conditions. I believe it would be a travesty to remove glutathione compounded by licensed pharmacies from public medical access. Thank you very much. I'm Dr. Paul Anderson.

(Pause.)

DR. STEVENSON: Hello. This is Takyiah speaking. Dr. Vaida, if you're speaking, you may be on mute.

Committee Discussion and Vote

DR. VAIDA: I'm sorry. I was on mute.

The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience. The committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

We will proceed with the question to the committee and panel discussion for glutathione. I would like to remind public observers that while this is open for public observation, public attendees may not participate, except at the specific request of the panel.

Today's question is a voting question. Dr. Takyiah Stevenson will provide the instructions for the voting.

DR. STEVENSON: Question 2 is a voting question. Voting members will use the Adobe Connect platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that voting will begin.

If you are a voting member, you will be moved to a breakout room. A new display will appear where you can submit your vote. There will be no discussion in the breakout room. You should select the radio button that is the round circular

button in the window that corresponds to your vote, yes, no, or abstain. You should not leave the "no vote" choice selected. Please note that you do not need to submit or send your vote. Again, you need only to select the radio button that corresponds to your vote.

You will have the opportunity to change your vote until the vote is announced as closed. Once all voting members have selected their vote, I will announce that the vote is closed. Next, the vote results will be displayed on the screen. I will read the vote results from the screen into the record. Next, the chair person will go down the roster, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you want to.

Are there any questions about the voting process before we begin?

(No response.)

DR. STEVENSON: Alright. Seeing none, I will hand it back to the chair to read the

question.

DR. VAIDA: Thank you.

For Section 503A bulk drug substances list for glutathione -- the vote -- FDA is proposing that glutathione not be included on the 503 Bulks List. Should glutathione be placed on the list?

If you vote no, you are recommending that 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 are no questions or comments concerning the wording of the question, we will now begin voting on the question for glutathione.

(No response.)

DR. STEVENSON: We will now move voting members to the voting breakout room to vote only. There will be no discussion.

(Voting.)

DR. STEVENSON: The voting has closed and is now complete. Once the vote results display, I will read the vote result into the record.

(Pause.)

DR. STEVENSON: Voting has closed and is now complete. The vote results are displayed. I will read the vote totals into the record. The chairperson will go down a list, and each voting member will state their name and their vote into the record. You can also state the reason why you voted as you did, if you wish to.

There are 8 yeses, 5 noes, 1 abstention.

DR. VAIDA: Okay. Thank you.

We will now go down the list and have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish. We'll start with the first person on the list.

Allen Vaida. I voted yes because I felt that it was not compelling evidence against its use or even with the safety aspect.

Dr. Gupta?

DR. GUPTA: Thank you. This is Dr. Anita Gupta, and I voted no. I felt that although glutathione is known to be stable, endogenous, and it's well characterized, there is unclear evidence, reproductive evidence, and developmental evidence in women, and toxicology studies that created some reasons for further evidence that was required. In addition, the information regarding lightning, I felt that there was need for further evidence. Therefore, I voted no. Thank you.

DR. VAIDA: Thank you.

Dr. Green?

DR. B. GREEN: This is Brian Green. I voted yes, and while I don't think that anyone's proven it necessarily does anything that they're saying it does, I don't think that there's a whole lot of harm there compared to a lot of already other available medications and supplements.

DR. VAIDA: Thank you.

Dr. Serumaga?

DR. SERUMAGA: Yes. This is Brian Serumaga from USP. I voted yes because there was sufficient

evidence presented that shows that glutathione can be physically and chemically characterized, and stable preparations can actually be made in a compounding pharmacy.

DR. VAIDA: Dr. Margolis?

DR. MARGOLIS: Yes. This is David Margolis. I voted no. I thought that there were ample opportunities for more compelling effectiveness or even efficacy data, and there just seemed to be just way too many indications and uses for something, and that it would be nice to know that it actually worked well in those indications.

DR. VAIDA: Dr. Rebello?

DR. REBELLO: Elizabeth Rebello. I voted no. I'm not convinced that the evidence was present in terms of efficacy, given the data that was presented.

DR. VAIDA: Dr. Gura?

DR. GURA: Hi. Kathleen Gura. I voted yes.

DR. VAIDA: Dr. Patel?

DR. PATEL: Hi. This is Kuldip Patel. I was on the fence on this one. I voted to abstain

so that I'm not swaying the decision one way or another. My concern was less so about the safety implications, but more about the mixed evidence of efficacy, especially among the variety of indications it is being considered for. Furthermore, once you make a decision to add an item to the list, or take it off -- in particular, adding it to the list -- there's no way for the used to be controlled as far as how, or when, or in what form it would be used, so I voted to abstain. Thank you.

DR. VAIDA: Thank you.

Dr. McElhiney?

DR. McELHINEY: This is Linda McElhiney. I voted yes. In my opinion, there are few serious and/or life-threatening conditions that would significantly benefit from glutathione therapy, and I think it should continue to be available to the compounders.

DR. VAIDA: Dr. Bogner?

DR. BOGNER: This is Robin Bogner. I voted yes to maintain patient access.

DR. VAIDA: Sandra Fusco-Walker.

MS. FUSCO-WALKER: This is Sandra Fusco-Walker. I voted no due to the lack of evidence.

DR. VAIDA: Dr. Evans?

DR. EVANS: This is Scott Evans. I voted no. I am concerned about the extremely broad range of indications for which this agent has been used without clear evidence of efficacy, and feel that it fails to address the point of lack of alternative therapies. Many of these conditions have well-established alternate therapies.

DR. VAIDA: Dr. Fensky?

DR. FENSKY: This is Tim Fensky. I voted yes.

DR. VAIDA: Dr. Calhoun?

DR. CALHOUN: This is Bill Calhoun. I voted yes. It's clear that the physical/chemical stability of this compound is fine. It's safe. There's really no risk to public health. It's an endogenous substance. Personally, I found the agency's review of the efficacy superficial and

narrow, and I found their conclusions dismissive of the positive data that existed because the outcome wasn't something that they were interested in looking at, or sometimes because of relatively small sample size. But I think the weight of evidence suggests that there are at least some uses for glutathione, so in order to maintain availability, I voted yes.

Adjournment

DR. VAIDA: Thank you.

It seems like we did have a mix vote on this one. I know that personally I feel that the indications are very broad, but I don't believe that there was enough data against the use of this.

We will now break for lunch. We will shorten our lunch, and let's try to reconvene at 1:45 Eastern time. Panel members, remember that there should be no chatting or discussion of the meeting topics with other panel members. Additionally, those panel members participating in the remaining topic discussion should plan to rejoin at 1:45 to ensure you are connected before

we reconvene. I meant to say 1:40. Thank you.

(Whereupon, at 1:15 p.m., the morning session was adjourned.)