FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Virtual Meeting

Wednesday, June 8, 2022

1:45 p.m. to 5:12 p.m.

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Takyiah Stevenson, PharmD

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Harvard Medical School
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Boston, Massachusetts

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Team Lead Compounding Pharmacist
Indiana University Health
Indianapolis, Indiana

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

Elizabeth Rebello, RPh, MD, FASA, CPPS, CMQ
Professor
Department of Anesthesiology and Perioperative Medicine
University of Texas MD Anderson Cancer Center
Houston, Texas

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

Allen J. Vaida, BSc, PharmD, FASHP
(Acting Chairperson)
Former Executive Vice President
Institute for Safe Medication Practices
Hatfield, Pennsylvania

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(Non-Voting)

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Pyxis Oncology

Cambridge, Massachusetts

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(Non-Voting)

Richard L. Green, BS Pharm, RPh, BCNP, FAPhA

Director of Radiopharmacy Practice

Cardinal Health Nuclear and Precision Health

Butler, Tennessee

TEMPORARY MEMBERS (Voting)

David N. Assis, MD

(Ammonium Tetrathiomolybdate Topic Only)

Associate Professor of Medicine

Digestive Diseases

Yale School of Medicine

New Haven, Connecticut

John N. Caviness, MD

(Ammonium Tetrathiomolybdate Topic Only)

Professor

Mayo Clinic

Mayo Clinic College of Medicine

Department of Neurology

Scottsdale, Arizona

Srinivasan Dasarathy, MD

(Ammonium Tetrathiomolybdate Topic Only)

Howard and Helen Trevey Endowed Professor of Medicine

Cleveland Clinic Lerner College of Medicine at Case Western Reserve University

Director, Liver Metabolism Research

Staff, Departments of Inflammation and Immunity and Departments of Gastroenterology, Hepatology

Cleveland Clinic

Cleveland, Ohio

David L. Eisenberg, MD, MPH, FACOG

(Ferric Subsulfate Topic Only)

Associate Professor

Associate Director, Division of Family Planning

Department of Obstetrics and Gynecology

Washington University in St. Louis School of Medicine

St. Louis, Missouri

Jorge A. Garcia, MD, FACP

(Ammonium Tetrathiomolybdate Topic Only)

Chair, Division of Solid Tumor Oncology

George and Edith Richman Distinguished Scientist Chair

Professor of Medicine and Urology

Genitourinary Medical Oncology Program

University Hospitals Seidman Cancer Center

Case Comprehensive Cancer Center

Case Western Reserve University

Cleveland, Ohio

Michael K. Lindsay, MD, MPH

(Ferric Subsulfate Topic Only)

Professor of Gynecology and Obstetrics

Director Division Maternal Fetal Medicine

Emory University

Atlanta, Georgia

Jorge J. Nieva, MD

(Ammonium Tetrathiomolybdate Topic Only)

Associate Professor of Clinical Medicine

Section Head, Solid Tumors

Keck School of Medicine

University of Southern California

Norris Comprehensive Cancer Center

Los Angeles, California

FDA PARTICIPANTS (Non-Voting)

Frances Gail Bormel, RPh, JD
Director
Office of Compounding Quality and Compliance (OCQC)
Office of Compliance (OC), CDER, FDA

Kathleen Anderson, PharmD
Deputy Director for Compliance and Operations
OCQC, OC, CDER, FDA

Gabrielle Cosel, MSc
Director
Division of Compounding Policy and Outreach (DCPO)
OCQC, OC, CDER, FDA

Rosilend Lawson, VMD, JD
Branch Chief
DCPO, OCQC, OC, CDER, FDA

Charles Ganley, MD

Director

Office of Specialty Medicine (OSM)

Office of New Drugs (OND), CDER, FDA

Daiva Shetty, MD

Associate Director for Pharmacy Compounding

OSM, OND, CDER, FDA

Marianne San Antonio, DO

(Lorcaserin Hydrochloride Topic Only)

Physician

Pharmacy Compounding Review Team

OSM, OND, CDER, FDA

Raquel Tapia, MD

(Ammonium Tetrathiomolybdate Topic Only)

Physician

Pharmacy Compounding Review Team

OSM, OND, CDER, FDA

Anam Tariq, DO, MHS

(Ferric Subsulfate Topic Only)

Physician

Pharmacy Compounding Review Team

OSM, OND, CDER, FDA

C O N T E N T S

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P R O C E E D I N G S

(1:45 p.m.)

Call to Order

DR. VAIDA: Good afternoon, and welcome back, everyone. Before we begin, Dr. Stevenson will introduce the new special government employees and FDA presenters for the afternoon topics.

DR. STEVENSON: Thank you, Dr. Vaida.

This is Takyiah speaking.

Dr. Assis, please introduce yourself.

DR. ASSIS: Hi. This is Dr. David Assis, associate professor of medicine and hepatology at Yale School of Medicine.

DR. STEVENSON: Dr. Caviness?

DR. CAVINESS: Hello. This is John Caviness. I'm professor of neurology in the Division of Movement Disorders in Scottsdale, Arizona. Thanks.

DR. STEVENSON: Dr. Dasarathy?

(No response.)

DR. STEVENSON: Dr. Dasarathy, if you are speaking you may be on mute in the Adobe room.

DR. DASARATHY: Can you hear me?

DR. STEVENSON: Yes, we can.

DR. DASARATHY: My name is Dasarathy. I'm a professor of medicine and transplant hepatology at the Cleveland Clinic. My expertise is ammonia and metabolism in multiple organs and ammonia utilization. Thank you.

DR. STEVENSON: Dr. Eisenberg?

DR. EISENBERG: Hi. Good afternoon. My name is Dr. David Eisenberg. I'm an associate professor in the Department of OB/GYN at Washington University School of Medicine in St. Louis, in the Division of Complex Family Planning.

DR. STEVENSON: Dr. Garcia?

DR. GARCIA: Good afternoon. Jorge Garcia. I'm a professor of medicine and urology and the chairman of hematology and oncology at University Hospitals Seidman Cancer Center and the Case Comprehensive Cancer Center in Cleveland, Ohio. I'm a GU medical oncologist.

DR. STEVENSON: Dr. Lindsay?

DR. LINDSAY: Hi. I'm Michael Lindsay, a

professor of OB/GYN, Emory University, Division of Maternal Fetal Medicine.

DR. STEVENSON: Dr. Nieva?

DR. NIEVA: Hi. This is Jorge Nieva. I'm a thoracic medical oncologist at the University of Southern California, Norris Comprehensive Cancer Center.

DR. STEVENSON: I will now introduce the FDA participants for the afternoon session.

Dr. Marianne San Antonio?

DR. SAN ANTONIO: Hi. Good afternoon. This is Marianne San Antonio. I'm a physician with the Pharmacy Compounding Review Team in the Office of Specialty Medicine, Office of New Drugs.

DR. STEVENSON: Dr. Tapia?

DR. TAPIA: Good afternoon. I am Raquel Tapia. I'm also a physician with the Pharmacy Compounding Review Team in the Office of New Drugs.

DR. STEVENSON: Dr. Tariq?

DR. TARIQ: Good afternoon. My name is Anam Tariq. I am also a physician in the Pharmacy Compounding Review Team of the Office of Specialty

Medicine in OND, Office of New Drugs.

DR. STEVENSON: Thank you very much. I will hand it back to the chair.

DR. VAIDA: Thank you.

We will now proceed with the FDA presentation on ammonium tetrathiomolybdate from Dr. Raquel Tapia.

FDA Presentation – Raquel Tapia

DR. TAPIA: Thank you.

Good afternoon. My name is Raquel Tapia. I am a physician with the Pharmacy Compounding Review Team in the Office of New Drugs. I will be discussing ammonium tetrathiomolybdate, referred to as ATTM throughout the presentation. I'd like to recognize the entire evaluation team, as well as the contribution of many other FDA colleagues who helped in this evaluation. Our special thanks to the Divisions of Hepatology and Nutrition; Neurology; and Oncology in OND.

ATTM was nominated for inclusion on the 503A Bulks List for use in compounding. It was evaluated for Wilson disease and copper chelation

therapy in breast, kidney, prostate, colorectal, esophageal cancer, and malignant pleural mesothelioma. The proposed dosage form is oral capsule, 20 to 60 milligrams.

These are the four factors we considered for our evaluation of ATTM. ATTM is the ammonium salt of tetrathiomolybdate, referred to as TTM, which is the active moiety of ATTM. This is a copper chelating agent sensitive to oxygen, but decomposes at room temperature, so it is likely to be stable only if protected from moisture and air when compounded as capsule.

Note that due to structural relevance, some discussion in this evaluation is from references that use the term TTM instead of ATTM. Such discussion is only to provide supportive information for the evaluation of ATTM.

ATTM has been studied in animal models where it has shown to form a complex with food protein and copper to prevent copper absorption. In rats, oral dosing decreased copper hepatic and renal uptake by increasing plasma retention of copper.

In dogs, oral and IV TTM increased serum copper levels, indicating copper mobilization from tissue. In sheep, prolonged subcutaneous dosing resulted in molybdate accumulation in multiple organs, including the brain and the pituitary.

Acute toxicity information was not found. A repeat oral dose-toxicity study in dogs showed that 1 of 10 dogs developed immune-mediated anemia and thrombocytopenia. In a dog model of copper-associated hepatopathy, CAH, copper levels decreased from baseline, whereas there was a significant increase in hepatic molybdenum. This suggests that TTM can decrease copper in some dogs with CAH.

The toxicology profile of ATTM has been described in the presence of copper. In weanling rats, ATTM with copper resulted in malformations of growing bones. In sheep, exposure to ATTM with copper resulted in fertility problems and marked morbidity, including atrophy of the pituitary and adrenal glands, testicular atrophy, and ovarian cysts. Genotoxicity and carcinogenicity studies

were not found.

In conclusion, TTM may be associated with an increased incidence of immune-mediated anemia and thrombocytopenia in dogs. Exposure to TTM with copper resulted in developmental malformations of growing bones, as well as pituitary, adrenal, and fertility problems in rats and sheep. No studies were found assessing genotoxicity or carcinogenicity potential of TTM.

We did not find PK data in humans. Two possible mechanisms of TTM with copper has been described. With food, it binds with copper and food protein, preventing copper absorption. This complex then mixes with bile in the intestine and is eliminated in the stools. Without food, it is absorbed into the blood where it binds to copper and albumin, making free copper unavailable for cellular uptake. It is then metabolized and eliminated via biliary excretion.

For the clinical evaluation and safety evaluation, we considered the following sources. We searched the FAERS database for reports listing

ATTM in an adverse events report. Sixteen reports were identified. The main reason for ATTM use was malignancy in 13 of 16 cases, and two reports on Wilson disease. Daily doses were variable. All cases reported serious outcomes, including death in a patient with hepatocellular carcinoma, which was determined unlikely related to ATTM.

These are the most common adverse events, AEs, which will be briefly described in the next few slides. Anemia, leukopenia, and neutropenia were reported. The onset was after 14 days after starting ATTM, suggesting a temporal association. Some patients required blood transfusion or hospitalization, and ATTM was discontinued in 7 patients. Five were rechallenged with a lower dose, and one had persistent anemia. Also reported were acute and chronic pulmonary embolic diseases and palpitations, but these were confounded by the underlying disease, concomitant medications, or limited by insufficient documentation.

Hepatic abnormalities were reported in the two patients with Wilson disease. One had elevated

AST and ALT 4 times the baseline after treatment with ATTM. The levels returned to baseline with temporary hold and dose production. The other patient had significant elevation in the liver enzymes one week after the dose was increased. AST and ALT peaked above 1000 and returned to baseline when ATTM was discontinued.

Now I will discuss clinical studies in Wilson disease. We reviewed 5 studies with safety assessments in patients treated with ATTM for 8 weeks. Doses ranged between 120 to 410 milligrams per day. The first study of 17 patients reported no toxicity.

The second study, which includes 16 new patients plus the 17 patients reported in the 1994 study, reported a patient who developed significant anemia with hemoglobin decrease from 13 to 7.5 grams. The anemia improved with cessation of ATTM and recurred with re-initiation. A bone marrow exam on this patient showed depression of hematopoiesis in the red blood cell line. In addition, 9 of the 16 new patients had elevated AST

at 5 weeks and returned to baseline with discontinuation of ATTM.

In the next study, which includes 22 new patients and the 33 patients from the previous two studies, 5 of the 22 new patients developed bone suppression with a decrease in the mean hemoglobin, WBC, and platelet count. Three patients had elevated liver enzymes with a mean ALT that was 10 times the normal by 5 weeks. Other liver enzymes were elevated as well. Per authors, bone marrow suppression and liver enzyme elevation can occur with rapid dose escalation.

This is a randomized-controlled study comparing ATTM with trientine. Anemia and neutropenia occurred in 4 patients on ATTM versus 1 patient on trientine, and elevated liver enzymes in 4 patients on ATTM versus zero on trientine. During follow-up, there were 2 deaths in ATTM and 4 deaths in the trientine group determined unrelated to the drug. In another study of 5 patients, 1 patient also developed anemia, leukopenia, and liver enzyme elevation with ATTM.

This resolved after withholding ATTM for 1 week and resuming at half the dose.

To summarize, available data on safety of ATTM in Wilson disease are limited to few small studies, mostly open-label, uncontrolled studies. But despite the paucity of data, studies have raised considerable safety concerns, particularly potential bone marrow suppression and liver dysfunction that appear to be related to ATTM use. There is also concern regarding the lack of safety data on the use of ATTM in pediatrics and pregnant women who have Wilson disease.

We found 7 clinical studies and a case report with safety assessment on ATTM in cancer treatment. Doses of ATTM, study size, and length of treatment varied. The most common AEs were bone marrow suppression and GI complaints. Dizziness and deep venous thrombosis, DVT, was also reported. It is unknown whether DVT may have been related to ATTM.

This is a case report of a female patient with cancer, self-treated with ATTM obtained via

the internet, who developed severe neutropenia and severe copper deficiency, as evidenced by a significant decrease in serum copper and ceruloplasmin levels. This case illustrates concern for potential misuse and clinically significant copper depletion associated with ATTM. Please note that copper is an essential trace element necessary for the activity of many key enzymes. Ceruloplasmin is a marker of copper status.

In conclusion, many safety concerns associated with ATTM use include bone marrow suppression and hepatotoxicity, which are potentially serious. There are also concerns of clinically significant copper removal associated with ATTM and the lack of safety data in pregnant women and children. There are approved therapies for the treatment of Wilson disease and cancer that have met established criteria for safety and effectiveness, and are labeled to inform their safe use.

Before switching gears to effectiveness, let

me give you an overview of Wilson disease and its treatment. Wilson disease is rare. It's caused by mutations in a copper transporter gene, leading to copper excess and accumulation most notably in the liver, the brain, and the eyes, causing organ damage. Signs and symptoms include chronic liver disease, neurologic abnormalities, and psychiatric disturbances. It is a serious progressive condition. It is fatal if untreated. The treatment goal is to reduce the amount of copper that has built up and maintain a copper level within a desirable range. It may be diagnosed in children.

The 2008 AASLD report recommends a chelating agent, either penicillamine, usually first line, or trientine, which was approved for patients unable to tolerate penicillamine, as initial treatment for symptomatic patients. For pre-symptomatic patients or those on maintenance, a chelating agent or zinc may be used. Treatment should be continued throughout pregnancy, some patients may need a liver transplant, and treatment is lifelong unless

liver transplant has been performed.

There are no approved drug products that contain ATTM. It has been studied for breast cancer under an IND, and an NDA was submitted seeking approval for Coprexa for the treatment of initially presenting neurologic Wilson disease. In 2008, the sponsor announced that the NDA was issued a Refuse to File letter by FDA, which cited, among other deficiencies, issues concerning adequacy of clinical effectiveness and efficacy, and requested for a short-term reproductive drug safety study in animals.

Now I'll summarize information on the effectiveness of Wilson disease. We've reviewed three phase 2 open-label studies with efficacy outcomes in a total of 55 patients presenting with neurologic symptoms. The main study objectives were to test the efficacy and toxic effects of ATTM. Neurologic assessments were performed using quantitative neurologic and speech scales at baseline weekly for 8 weeks, then yearly.

ATTM was given daily, orally for 8 weeks,

followed by oral zinc as maintenance. The study found that only 4 percent of the patients showed neurologic deterioration, and there was gradual improvement over time, however, these studies are of limited utility because the duration of treatment was too short. It is difficult to evaluate efficacy based on an 8-week trial that is looking for evidence of neurologic deterioration in a chronic neurologic condition like Wilson's. Also, these are single-arm studies, and interpretation of efficacy is difficult without a comparator. Also, the scales used are of limited utility, as they lack validation. The studies are also limited by a significant amount of missing data.

The next study compared ATTM to trientine on neurologic worsening. Patients were treated for 8 weeks with either ATTM plus zinc or trientine plus zinc. All patients continued zinc maintenance after this study.

Neurological assessments were done with the same scales as the previous 3 studies, weekly for

3 weeks, then yearly for 3 years. The authors found neurologic deterioration in one of 25 patients in the ATTM group versus 6 of 23 patients in the trientine group. However, like the previous studies, this study is also of limited utility because the treatment duration was too short and the scales lacked validation, so the clinical relevance is unclear.

Next is an uncontrolled longitudinal study in 5 patients also treated with ATTM, 120 milligrams, followed by oral zinc for maintenance. Note that two additional neurologic scales were used for their neurologic assessment. The study reported neurologic improvement in all patients by 3 months. But again, this is an open-label study, only 5 patients, short duration of treatment, and this study should be confirmed in a larger randomized trial.

Now moving on to effectiveness in cancer, here are important points to help us understand ATTM nomination as a copper chelator in cancer treatment. Cancer involves abnormal cell growth

along with invasion, dissemination, and metastasis. It is hypothesized that progression of cancer cells is dependent on copper. Copper levels in cancer cells are higher than in normal cells, and copper is an important co-factor for angiogenic growth factors and cytokines that are critical for tumor angiogenesis. Angiogenesis is the formation of new capillary branches from existing blood vessels and is controlled by a balance on stimulating and inhibiting factors.

We identified two studies of ATTM in breast cancer patients at high risk for recurrence. The first one is an open-label study, single arm, in 39 patients. Standard cancer treatment was completed at least 6 weeks prior to this study. Concurrent hormonal therapy was allowed. The treatment was for 2 years or until relapse.

The authors found copper depletion in 75 percent of the patients by 1 month and reduced bone marrow-derived endothelial progenitor cells, EPCs, which are considered critical for metastatic progression. Sixty-nine percent of the patients

had no relapse, and the authors concluded that ATTM may ultimately prevent relapse, but that a larger randomized trial would be needed to confirm this.

The other study is also open label, single arm in 75 patients. ATTM treatment was for 2 years or until relapse; and, again, standard cancer treatment was completed prior to study, and concurrent hormonal therapy was allowed. The study showed that copper depletion correlates with reduced EPCs and other biomarkers, and event-free survival was 73 percent with an overall survival over 84 percent at a median follow-up of 6 years.

The authors concluded that while these results are encouraging, they need to be confirmed in a larger randomized, placebo-controlled trial. So these two studies do not provide adequate evidence that ATTM contributes to clinical response because the trials were single arm and patients continued to receive other cancer therapy.

The next two studies are also single arm, evaluating TTM anti-tumor activity and the effect on several angiogenic factors. One was in patients

with advanced kidney cancer, where the patients received standard therapy, cancer therapy, at least 4 weeks prior to the study and received TTM for 6 months. Overall, the 6-month progression-free rate was only 31 percent, and the authors concluded that TTM alone showed no efficacy in patients with advanced kidney cancer.

The other study in patients with hormone-refractory prostate cancer did not show any significant change during therapy in the levels of angiogenic factors tested. The study was terminated after enrollment of 19 patients due to cancer progression. The authors concluded that copper depletion with TTM did not delay disease progression in patients with asymptomatic metastatic hormone-refractory prostate cancer.

The next study is for malignant pleural mesothelioma, MPM. This is a phase 2 study, evaluating the effect of copper depletion on progression and survival after cytoreductive surgery in 30 patients compared to 169 historical controls. The study showed a slight advantage in

terms of time to progression for stages I and II, 20 months versus 10 months, but the time to progression for stage III, a median of 7 months, was no different from historical controls.

The authors concluded that TTM has some anti-angiogenic effect in MPM after surgical resection, but also concluded that the study has potential for bias because it is not randomized, and recommended validating the study with a larger randomized trial.

The next two are single-arm studies, one in metastatic colorectal cancer and the other in esophageal cancer. A pilot study on 24 colorectal cancer patients evaluated TTM in combination with chemotherapy. The authors found no correlation between baseline serum cytokine levels and time to progression. Tumor progression was seen in all patients within 5 months.

In the esophageal cancer study, 69 patients received TTM for 4 weeks after standard cancer treatment. A comparison was made with 69 historical controls. The authors found no

statistically significant difference in disease-free or overall survival after 3 years and no association between decreased level of ceruloplasmin and recurrent-free survival or overall survival.

In conclusion, there is insufficient information to support the effectiveness of ATTM for the treatment of Wilson disease and as copper chelation therapy in the various types of cancers we evaluated. There are currently available FDA-approved therapies with established efficacy for the treatment of Wilson disease and for these cancers.

Lastly, this is what we found on historical use of ATTM in compounding. It has been used since 1984. It has been evaluated in various other conditions, in addition to Wilson disease and cancer. One outsourcing facility reported compounding ATTM capsule in 2017, and an internet search reveals 4 compounding pharmacies within the United States. One Australian compounding pharmacy advertised compounding ATTM capsules. The

International Journal of Pharmaceutical Compounding published compounding formulations for ATTM 20-milligram and 50-milligram capsules, but there is no compounded drug product monograph for any dosage form in the U.S. Pharmacopeia or the NF. In conclusion, there is evidence of the historical and current use of ATTM in compounding both within and outside the United States.

To summarize our evaluation, ATTM can be characterized, but it is likely to be stable only if protected from moisture and air when compounded as capsules. Regarding safety, in nonclinical studies, ATTM resulted in malformation in growing bones. Clinical studies in adults have raised concerns of liver toxicity and bone marrow suppression. Other potential concerns include significant copper removal and a lack of safety data in pregnant women and children.

Likewise, there is insufficient information to support the effectiveness in Wilson disease and as chelation therapy in cancer. There are available FDA-approved therapies with established

efficacy for the treatment of Wilson disease in cancer, and the existence of approved drugs to treat these serious conditions weighs against including ATTM on the 503A list for compounding. There is evidence that ATTM is used in compounding as an oral formulation both within and outside the United States.

After considering the information currently available, a balancing of the four evaluation criteria weighs against ammonium tetrathiomolybdate being added to the list of bulk drug substances that can be used in compounding under 503A of the FD&C Act. Thank you very much, and 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. 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.

Dr. Nieva, do you have a question?

DR. NIEVA: Thank you. This is Jorge Nieva from USC.

Dr. Tapia, was the bone marrow suppression that was seen with ATTM treatment associated with the typical vacuolization of copper deficiency or was the cytopenia felt to be due to some mechanism other than generation of copper deficiency?

DR. TAPIA: Thank you for your question.

In these studies, I believe that the quality assessment considered the impact of ATTM on copper, so it may be related to copper depletion rather than direct toxicity of the molecule on the bone marrow.

DR. NIEVA: Thank you. And just to follow

up, you mentioned in the studies evaluating the efficacy of ATTM that the treatment duration was too short to be able to evaluate its effect. However, you also stated that the patients were treated with another copper chelator as maintenance therapy, which was oral zinc and that treatment duration was 8 weeks. And in slide 30, you said that in one study, 75 percent of patients were depleted of copper within one month.

Can you explain to me why you think that a strategy of what sounds like copper depletion followed by maintenance therapy was too short to evaluate the impact of copper deficiency? Thank you.

DR. TAPIA: Yes. Thanks again for your question. I believe you are referring to the studies on Wilson disease. Give me one second to get that slide up. I think it's slide 25.

DR. NIEVA: I can't recall the slide number for the --

DR. TAPIA: Yes. I think they can pull it up for us, slide 25.

Yes. For the treatment of Wilson disease, Wilson disease being a chronic neurological condition, the treatment of 8 weeks of therapy is kind of too short if we are looking for evidence of effectiveness in a chronic condition like Wilson disease. I would ask, if possible, from our colleagues in the neurology division, if they can provide additional comments on that.

DR. PODSKALNY: Hello. This is Dave Podskalny. I'm a movement disorders neurologist in the Division of Neurology I at the FDA.

Sure. Neurologic symptoms are uncommon in Wilson's disease. Somewhere estimates vary between 30 and 60 percent, and Wilson's is already a rare disease. Generally, there's not a large number of controlled studies or active comparator studies for neurologic symptoms of Wilson's disease. However, what's been learned is that patients who present with neurologic symptoms, about half to 65 percent never improve -- excuse me; about half to 65 percent have symptoms. Those patients may never improve despite years of treatment. I think

studies have gone out to 4 to 5 years.

Some of the patients improve, depending, in part, how long their symptoms have been present, [indiscernible]. But there is no timetable for either getting better or worsening. Sudden worsening was thought to occur because of mobilization, too much copper into the circulation, [indiscernible] deposits into the tissues, including the brain.

There is no clear theory or mechanism for people who continue to worsen or show no improvements. There are many mechanisms for that such as not [inaudible – audio gap] for Wilson's disease.

DR. NIEVA: Thank you. I'm a bit confused, perhaps. Is the FDA position that this drug is not an effective copper chelator, or is it the position that this product has concerning off-target toxicity?

Dr. Tapia, maybe you would be the best person to ask that.

DR. TAPIA: Yes, I guess I can start. Thank

you for your question. I can start, and then, again, our colleagues in hepatology and neurology, please feel free to jump in for additional comments.

Available data on the effectiveness of ATTM, like we mentioned, in Wilson disease are limited to few, mostly open-label, uncontrolled studies of short duration. But a significant issue in the evaluation of chelating drugs for the treatment of Wilson disease is the direct demonstration that the drug treatment results not only in copper mobilization into the circulation, but removal of copper from the body and reducing the pathologic overload of copper.

As discussed in the nonclinical session, copper bound to TTM and protein is primarily eliminated via the biliary system in the feces, however, there is no clinical data to confirm this. While available data may allow evaluation of the ability of ATTM to mobilize copper into the circulation, currently available data is insufficient to allow the evaluation of ATTM's

ability to remove and eliminate copper from the body.

We cannot conclude from the studies that the reduction in the neurologic speech scores translate into an improvement in how the patient feels, functions, or survives, so it is also unclear how clinically meaningful within patient's changes in the neurologic scores are; for example, how clinically relevant a change of 5 points in a 0 to 37 neurologic scale, how critically relevant that is.

So there are concerns -- not concerns. There is limited information or questions that we don't know yet in terms of how ATTM works, and there are also the safety concerns that we mentioned.

Any additional information or comments from neurology, please, or hepatology?

DR. MAKAR: Hi. This is George Makar from the Division of Hepatology and Nutrition. Can you hear me ok?

DR. TAPIA: Yes, we can.

DR. NIEVA: Yes.

DR. MAKAR: I think from a hepatology perspective, with the current copper chelators such as trientine and D-penicillamine, you're able to monitor the amount of copper excretion in the urine. So not only do you monitor the non-ceruloplasmin down in copper, which has its limitations, but you can also follow 24-hour urine-copper excretion to sort of confirm that you're treating copper and to be able to monitor things in an ongoing basis.

With zinc, obviously, it does work differently with the metallothionein, but, in general, the zinc is typically reserved for asymptomatic or for those who have been previously de-coppered, and it's not nearly as profound as a copper binder, and it doesn't work in the same way as D-penicillamine or trientine.

The concern for trientine is that because, ostensibly or theoretically, of its relief that's excreted in a biliary process and fecal process, there's not an easy way to monitor copper excretion

with the use of this drug, and there isn't a clear-cut that you can see the concern of abnormal liver enzymes or cytopenias; that often they can occur soon after initiation of therapy.

What we don't know is, would you need to -- some of these can occur as early as 2 weeks into therapy, so would subjects have to be continually monitored every 2 weeks while they're on this therapy? How would dose adjustment be made for copper overload versus copper deficiency, short of manifestation of toxicity, of either too much or too little copper? And we don't really have data that guides us in a standard-of-care or an objective manner in the same way as we do with the current copper chelating agents.

I don't know if that adequately answers your question or not, but happy to answer any follow-up questions.

DR. PODSKALNY: Hi. This is Dave Podskalny again from neurology. The trials that were done were open label, and I can't under-emphasize the amount of missing data over the course of time,

even over the 8-week follow-up period, but then there was a longer follow-up period. There were people missing baseline assessments, and over the course of 8 weeks, additional people had not had assessments done.

So, in essence, you're dealing with about half the data from the available number of patients; so, really, there isn't a great database to pull from. There are patients that worsened during that time. There are patients that fluctuated by a point or two at different time points.

Without having data on the reliability and validity of those instruments over time, it really is difficult to understand, even among the patients who appeared to get better, how to interpret that. So it really isn't convincing evidence and even reliable information that we're staking our claim on.

DR. NIEVA: Thank you. That concludes my questions.

DR. VAIDA: Thank you.

Does Dr. McKinnon from the FDA have a comment?

DR. McKINNON: It was already addressed. Thank you.

DR. VAIDA: Thank you.

Dr. Assis?

(No response.)

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

DR. ASSIS: Yes. Hi. Dr. Assis from Yale. I have a question just regarding -- and I apologize for not having experience with the compounding arena quite as much, but my understanding of the bulk compounding bar is that these have a potential role for patients who have clinical needs that cannot be met through the standard drug approval process, and clearly this compound would not be nearly close enough to any degree of standard evaluation given the limited data.

But I guess I don't have a baseline, from prior experience, as to how incomplete the data is, and missing data, for this compound, even compared

to other substances that are being debated under the bulk substances list because I don't have a good benchmark for that. I agree that there's a lot of missing data, but how far in a subjective asking is this from the typical standard that's met under this provision? Thank you.

(No response.)

DR. VAIDA: Anyone from the FDA?

DR. PODSKALNY: Hi. This is Dave Podskalny. In terms of the available data, it's the ability to assess a potential benefit from the known risks, and I think the known risks are potentially serious, as laid out in the slides, and the benefits are either not interpretable or not adequately studied to determine that there's any benefit to the patient in terms of neurologic symptoms.

I hope that addresses your questions.

Is there any follow-up?

DR. ASSIS: No. Thank you.

DR. VAIDA: Dr. Garcia?

DR. GARCIA: Thank you. Jorge Garcia,

University Hospitals, Seidman Cancer Center; just a comment and a question for the FDA.

As a drug developer, it's really hard to understand the sample size that was presented in the clinical trials by your group at the FDA, so it's hard for me as a clinical investigator to really make too much when you have a sample size of 5, 40, and the like.

But perhaps my bigger question is, in a couple of the initial slides from the FDA, it was mentioned that in animal trials there was some concerns about teratogenesis and malformations, yet in the existing data presented by the FDA, there was no comment, and the bulk of the AEs that were reported appeared to be hematologic in nature, as Dr. Nieva addressed before.

So my question for the FDA group is, what is the benchmark or the requirements that the group uses when looking at bulk substances that can be used in compounding?

DR. BORMEL: Dr. Vaida, this is Gail Bormel. I can answer some of those questions --

DR. VAIDA: Sure.

DR. BORMEL: -- if that's ok.

When we're evaluating the bulk drug substance for inclusion on the 503A Bulks List, we look at four different criteria. We look at the chemistry and the characterization of the bulk substance. We look at the safety of the bulk substance when made into a certain formulation to treating uses. We look at the effectiveness, and then we also look at the historical use.

So it's a balancing of these different criteria; there's not a formulation. But what I thought I heard from our experts in the review division is that with this particular substance, there are safety concerns, and the safety concerns do not outweigh -- I'm sorry. The safety concerns are such that they do outweigh any benefit that they're seeing in the studies that are represented, and if I'm wrong on that, I would like the review division experts that have spoken to say something now.

So we are weighing these four different

criteria, and it's a judgment on what we're seeing, specifically whether it can be made into a compound, whether there are a lot of safety issues or some safety issues that are important and significant, and balancing that with any effectiveness and also the history of use. I hope that helps.

DR. TAPIA: This is Dr. Tapia. Again, in addition to that, I would ask that we also take into consideration other factors such as the disease itself or the condition; for example, whether this is a serious or life-threatening condition, and also whether there is approved alternative therapies in our assessment.

DR. GARCIA: Can you or your group at the FDA -- again, this is Dr. Garcia, University Hospitals, Seidman Cancer Center. Can you specifically comment as to, again, what are the benchmark requirements? I understand they complete the AE profile of an agent, but specifically I'm asking for genotoxicity or carcinogenicity in the TTM compound.

DR. GANLEY: Hi. This is Charley Ganley. I'm not sure what you mean by benchmark. All of the things that we are reviewing are unapproved drugs In some instances there is going to be that information available, and others, they're not. We take that into account, and in some circumstances, depending on the condition being treated, that becomes more important than other situations.

So I think it's an issue for the committee to weigh. Obviously, if it's a short-term treatment, that may weigh differently than if this is the long-term treatment. If the population's going to include young women who have childbearing potential, that weighs into the decision.

So there is really no benchmark here. This is the data we have. It's not data generated by us; it's data that we've obtained from the literature or from the nominator. So the committee has to weigh these things into their considerations.

Obviously, if we had that data and it showed that there was a potential problem, that would

weigh heavily against it. The issue really comes down to, if we don't have that data, does that weigh against it; and if so, how much? But that's something the committee has to take into their deliberations, and I suspect that the opinions are going to vary quite a bit among people.

DR. GARCIA: Thank you. That's the end of my question.

DR. VAIDA: Thank you.

Dr. Gura?

DR. GURA: Hi. Kathleen Gura, Boston Children's Hospital; a clarifying question.

ATTM received orphan designation status for a treatment of Wilson's disease. How will the decisions this committee makes impact that orphan designation status? Would patients still be able to get it because it's of that status?

DR. GANLEY: This is Charley Ganley again. Let me just try to clarify. I'm not sure what people think of orphan designation status. You may get orphan designation status, but that's more important if the drug is approved and has to do

with the exclusivity and things like that.

So simply because it has orphan status has no meaning that it's been determined that it's effective for safe therapy. All that information has to be collected yet. The impact is greater if someone submits a new drug application or a BLA application and it essentially gets approved, but it's not going to have a status effect on the -- the orphan designation status has no bearing here.

DR. GURA: Okay. Thank you very much.

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

DR. DASARATHY: Yes. Can you hear me?

DR. VAIDA: Yes.

DR. DASARATHY: Okay.

I heard a lot about the copper. What I did not hear was what would be the consequences of the ammonium salt that is going to be provided? The ammonium salt has a number of effects, even in people who have well-compensated liver function, so it can affect skeletal muscles, which can affect

protein responses in the astrocytes.

So from the entire presentation, I didn't see anything about the potential toxicity of the associated ammonia. So the assumption is that the ammonium component of the tetrathiomolybdate is not going to have any metabolic or functional effects. I'm done. I'm going to mute myself.

DR. TAPIA: This is Dr. Tapia, and thank you for your question. We did not evaluate the specific issues associated with the ammonium salt.

DR. DASARATHY: But would that not affect the responses? Because even in malignant cells, ammonium increases or decreases [indiscernible] in a context-dependent manner, and it could affect the responses to other chemotherapeutic agents, as well as growth of the tumors.

So I'm just curious what unanticipated effects could occur because of the ammonium part. I tried to look up if there is any of the salt tetrathiomolybdate, which has been studied, which can allow us to dissect out the effect of the ammonium versus the non-ammonium salts of the

tetrathiomolybdate. Thank you.

DR. TAPIA: Yes. Thank you, again, for your question. Like I mentioned, we did not look into that specifically. I would allow our colleagues from our divisions of neurology or hepatology to have additional comments on that.

DR. DASARATHY: Thank you.

DR. PODSKALNY: Hi. This is Dave Podskalny from neurology. The studies that you're talking about would be very difficult to do, at least in the context of Wilson's disease, because the patients that were accrued, or the case series that was accrued by Dr. Brewer, started in 1994 and span well over a decade to collect 55 cases.

So being an uncommon disease, it becomes very difficult to study specific questions or compare formulations. There are other salts that have been looked at mainly because the ammonium salt is so unstable, but I don't know to the degree of which they've been compared directly, if they have been at all.

DR. DASARATHY: Thank you.

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

DR. ASSIS: Yes. Hi. Dr. Assis from Yale. I do have a very quick question, which I don't believe is necessarily directly related, but I just would like to ask. I understand that this meeting is to discuss bulk compounding, and the bar, again, still needs to be met for safety, of course, and efficacy. But these are primarily for compounds that may never see the light of day for patients.

I do know there is a phase 3 study of tetrathiomolybdate, which is in phase 3. I think there's probably a little bit of time, still, until that data becomes available. And even though that's a whole separate approval and regulatory pathway, it appears to me that the intent from the investigators or the company would be for that drug to be proposed as a more stable version of this ATTM, which is I think recognized as a problem.

So I'm not entirely sure I understand the implications of approval for this, given the limited safety data and some of those concerns,

especially if there is a medication that's being tested as a more stable -- and I won't say more safe -- version of this. So I wonder whether there is a need to feel pressed against the wall for this approval, given the fact that there is something that's currently being evaluated in a more rigorous fashion. Thank you.

DR. VAIDA: Dr. Bormel, do you have a comment?

DR. BORMEL: No. I apologize. I just forgot to clear my raised hand.

DR. VAIDA: Alright. Thank you.

We'll now proceed with the nominator presentation. We have one presentation from Dr. Mark Rosenberg, who is speaking on behalf of Pharmacy Solutions.

DR. ROSENBERG: Thank you.

First of all, I just want to make sure everybody can hear me.

DR. VAIDA: Yes.

DR. ROSENBERG Okay. Thank you. Before I begin, if I can address a question to Dr. Tapia.

This ATTM has been compounded for, certainly, I guess in excess of 20 years, and I'm just going to raise a question about safety. And, certainly, we know many different substances that are over the counter that if abused or not taken appropriately can cause many problems, including death.

How many deaths were you able to find were related to ATTM since it's been compounded?

DR. TAPIA: Yes. Thank you for your question, Dr. Rosenberg. My evaluation of this substance, I did not find any particular death that was directly attributed to the drug.

DR. ROSENBERG: Thank you. That answers my question. Thank you.

DR. TAPIA: You're welcome.

Nominator Presentation – Mark Rosenberg

DR. ROSENBERG: Okay. I will proceed now and talk about the safety and efficacy of ATTM.

As you can see from this slide, there's increasing interest from several research groups in modulating copper bioavailability as a therapeutic

strategy, and certainly you can see these published articles in reputable journals. It really is generating a lot of interest now because copper plays a very important role in the tumor microenvironment.

I don't want to spend much time -- because I don't have much time -- but this is a pictorial of the hallmarks of cancer as delimited by Dr. Robert Weinberg from MIT, and coming out from this circle are many different mechanisms of action through which cancer progresses and eventually metastasizes.

Copper is involved and instrumental in affecting many of these processes, including promoting angiogenesis; mitochondrial oxidative phosphorylation; affecting the tumor microenvironment; affecting the stromal and collagen remodeling; as well as promoting oxidative stress, invasion, migration; and most recently demonstrated that there's a direct correlation between the amount of copper in the tumor microenvironment PD-L1 expression.

What you'll see on the right is the tetrathiomolybdate molecule bound to copper, and what we do know and what's been demonstrated is that ATTM will inactivate copper chaperones. For example, Atox, antioxidant protein 1, is found in the cytoplasm and often overexpressed in cancer cells. What it literally does is it will chelate copper and shuttle it to other metalloenzymes that are important for proliferation and progression.

What ATTM does is it will bind stably to the complex of Atox 1 with copper and prevent that shuttling. As you know, there's been a phase 3 trial. There's a phase 3 trial in Wilson's disease underway, as was recently stated. Mouse models of cancer have shown tumor regression, and phase 1 and 2 trials in overt cancer have shown stable disease in humans at best response.

Keep in mind that it really does depend on how low you get the ceruloplasmin. A phase 2 study in high risk for recurrent breast cancer, that's been underway for a while with an expected completion date of approximately June of '23.

Looking at some of the safety data of TM in advance and high-risk cancers, you can see TM was used alone in stage 4 renal, stage 4 prostate, resected mesothelioma, resected esophageal, and in combination with a 5FU-based regimen in stage 4 colorectal cancer. The most prominent side effects that we see are reversible neutropenia, and when I say reversible neutropenia, almost all the time with simply cessation of the drug or decreasing dose, neutropenia rapidly resolves.

This is a preclinical model in mice, the MMTV-Her2neu expressing mouse model that was randomized to TM for 180 days versus water control. What is not depicted in this graph is that in the control group, 67 percent of the mice have palpable mammary tumors at 180 days, whereas only 13 percent of the TM group did.

As you can see here, the control mice actually developed lung mets, or lung metastases, at day 205, but the TM group did not. However, when TM therapy was withdrawn, the mice developed lung mets at a median of 2 weeks later. So they

concluded that TM therapy prevented the development of overt metastases in this model only while they were on TM.

The concept is that targeting the tumor microenvironment through a copper depletion strategy can prevent metastases, and TM is safe and well tolerated. A phase 2 study was initiated with TM in those individuals with high risk for recurrent breast cancer, and one of the goals was to embed significant amounts of science with the study to understand the mechanism of action.

In this pilot trial, they included breast cancer patients with high risk of relapse and no evidence of disease, so these patients included stage 2, but they had to be the most aggressive, triple-negative breast cancer patients. They included stage 3 and stage 4, but if there were stage 4, they had to have NED or no evidence of disease. No evidence of disease was confirmed by a physical exam; laboratory studies, including tumor markers; and imaging: CT, chest, abdomen and pelvis with bone scan or PET/CT scan. These individuals

had to have completion of standard therapy before they were initiated on TM.

The patients received daily oral TM for 2 years to achieve a ceruloplasmin target level of less than or equal to 17 milligrams per deciliter. The primary endpoint here was endothelial progenitor cell expression of VEGFR2 quantifying that; secondary endpoints for progression-free survival, overall survival, and hematopoietic cell expression of VEGFR1, as well as looking at adverse events and circulating markers in the tumor microenvironment.

The accrual for this was completed in 2014. As far as examining the patients, they were examined every 4 weeks, which was one cycle with physical exam; again, basic labs, including CBC, comprehensive metabolic panel, tumor markers, ceruloplasmin level, as well as flow cytometry for bone-marrow-derived progenitors; as well as other research blood, which is banked. In addition, imaging studies with either CT, chest, abdomen, pelvis, and bone scan, or PET CT, was performed

every 6 months.

There were 75 patients enrolled. One dropped out prior to treatment leaving 74, and 24 patients discontinued before two years. The reasons for discontinuation were 12 had developed recurrent disease, three had toxicity, and toxicity was one patient had diarrhea, another patient had a grade 3, B-12 associated anemia, and the third patient had febrile neutropenia and decided not to continue. As far as the nine others, logistically, they just were not able to make the monthly appointments.

Fifty-one patients completed two years of ATTM or TM therapy, and then 39 patients continued TM therapy on extension only. Of those 39, 25 patients were in the adjuvant group, meaning stage 2 or 3, whereas 14 patients were stage 4 NED. As of March 2020, 16 patients continued on TM, 14 of them were stage 4 NED, whereas two of them, it was not clear whether they were stage 3 or stage 4. This study was closed due to the loss of drug supply. The patients transitioned to non-GMP grade

material after that. On the right is just simply showing the demographic variables, as well as where the cancer was located, and of course the subtypes of cancer as well.

Perhaps the most important slide to look at here is that the grade 3 or 4 adverse events were less than 3 percent; and remember, a cycle was 4 weeks, so they looked at a total of 3,478 cycles and, again, it was less than 3 percent. But the most common was neutropenia, again, which was reversible with either cessation of the drug or decreasing dose. The most common side effect that includes all adverse events was sulfur burps.

Then we look at survival, and going to a median follow-up of 9.4 years, the event-free survival was 71.4 percent, with overall survival being 64.7 percent; looking at breast cancer specific survival, approximately 80 percent at this follow-up of 9.4 years. When we look at event-free survival by molecular subtype, including triple-negative Her2neu positive and luminal, there's really no difference in outcome, based on

the subtype, all hovering at around 70 percent.

Then we look at the event-free survival in the adjuvant group, meaning stage 2 and 3, again with a median follow-up of 9.4 years, it was 79.3 percent. Then coming to the right, looking at the stage 4 NED by molecular subtype, really what was very impressive is the triple-negative breast cancer group. You'll see the triple-negative breast cancer group had an event-free survival of 59.3 percent, which is amazing given the median survival for stage 4 TNBC is about 9 to 11 months. You can see the best event-free survival was in the luminal, 63.6 percent, and then Her2neu, 50 percent.

Then we look at event-free survival of the triple-negative breast cancer patients by stage. The stage 2 triple-negative breast cancer was 100 percent event-free survival; stage 3 was 79 percent and, again, what is amazing is you look at the stage 4 event-free survival, it was 59 percent, which is extremely rare given the median survival of TNBC, and certainly stage 4

TNBC.

So the scientific correlatives here in the copper-depleted patients, reduction in the endothelial progenitor cell that were expressing VEGFR2 was seen. There was a reduction in lysyl oxidase like 2. There was normalization of the collagen microenvironment, and interestingly, there was improved event-free survival in the adjuvant patients whose primary tumors were expressing antioxidant 1 copper chaperone. Again, that is the cytoplasmic chaperone for copper.

In the preclinical models, there was no effect in primary tumors, but there was a decrease in lung mets and, again, those lung mets showed marked reduction in lysyl oxidase and collagen remodeling. Another interesting finding is there was reprogramming of the metabolic environment, so there was a shift away from mitochondrial oxidative phosphorylation towards glycolysis. Also, there was a reduction in myeloid-derived suppressor cells in the primary tumors of the TM treated mice.

The next step, there is a randomized phase 2

study in high risk for recurrence, triple-negative breast cancer patients underway, plannings underway, and supported by multiple groups: the NCI Research Project Grant, the NCI NExT Program; Gateway Foundation; Breast Cancer Research Foundation; Translational Breast Cancer Research Consortium; as well as philanthropic donors.

An investigation is also underway in high-risk, non-small-cell lung cancer, both preclinical with clinical trial development as well, and the BRAF-V600 mutated melanoma with the goal, again, of course being to expand the correlative science in the completed phase 2 study in breast cancer that will be completed next June. That concludes my talk.

DR. VAIDA: Thank you, Dr. Rosenberg.

DR. ROSENBERG: Thank you.

Clarifying Questions from the Committee

DR. VAIDA: We'll now take clarifying questions for nominator presenter. Please use the raise-hand icon to indicate 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. If you wish for a specific slide to be displayed, please let us know the slide.

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

Dr. Nieva?

DR. NIEVA: Thank you, Dr. Rosenberg. One concern that has been expressed with ATTM versus alternative copper chelators is that there's no effective monitoring strategy given that it's stool absorbed.

Can you comment on the current monitoring strategies for copper levels and copper deficiency development in patients who are using this compound, and how it differs from that using other chelators? Thank you.

DR. ROSENBERG: Thank you. Thank you for your question. I can tell you from personal

experience that I've been using this substance in high-risk individuals with cancer for approximately 14-plus years, and what I have been doing is monitoring the CBC comprehensive metabolic panel and ceruloplasmin levels every 4 weeks at a minimum. And I say at a minimum, because if I adjust doses, I may check their blood levels a week later or 2 weeks later.

The most common side effects from a hematologic standpoint we'll see are the leukopenia, neutropenia, and then of course mild anemia. So the way I've been adjusting it is if I see that the white count is getting significantly below 3, we simply back off. I've treated hundreds of patients, and I have had nobody hospitalized, and of course no adverse effects. What I can see is the best way to monitor this for safety is simply too frequently monitor the cell counts and the ceruloplasmin.

Now, I will tell you something else that I do. When copper is depleted, it actually causes a functional iron deficiency as well. That is

delineated in the literature, but the mechanism is not clearly worked out. But copper and iron do work together in some fashion, so what I always do is before I start these patients on treatment, I also measure their serum irons because if they're iron deficient and you make them copper deficient, you can expect to cause maybe more significant problems with anemia.

But as far as really quantifying how much copper is being excreted, I would pose the question of how important is that? In other words, if we're keeping the cell counts adequate, and the patients are feeling well, and either the cancer is stable or it's not recurring, I think that's the primary objective.

I don't know if I answered your question adequately, but please let me know.

DR. NIEVA: Thank you.

Just in follow-up, can you give me a sense of how much of the use of this agent is done under investigational purposes? Within the context of a defined clinical trial under human subject

supervision, what percentage is being used in Wilson's disease and what percentage is being used off label as a cancer therapy?

DR. ROSENBERG: Sure. And I am going to give you my guesstimate on this because I'm not aware exactly what the numbers are. But I would suspect most of the use, and I say most, that well over 90 percent of the use is just being used off label and not under a formal trial.

There are a few reasons for this. There's not a lot of interest. I think most physicians are really unaware of this substance, and one of the reasons is, of course, it is not an FDA-approved drug. So most of the physicians that I know that are using this -- and I don't know how many there are, but they're simply using it in a non-controlled fashion, meaning not under a clinical trial. But having said that, it's been used probably since at least the '80s.

DR. NIEVA: Thank you. That concludes my questions.

DR. ROSENBERG: Thank you.

DR. VAIDA: Thank you.

Dr. McKinnon from the FDA, do you have a comment?

DR. McKINNON: Thank you, Chairman Vaida. Dr. Osgood from OND would like to be recognized for a comment, please.

DR. OSGOOD: Yes. Hi. This is Dr. Osgood. I'm one of the clinical team leaders in the breast cancer division in the Office of Oncology Drugs. I just wanted to offer a perspective on some of the clinical data that was submitted.

Basically, this is data from single-arm trials where multiple agents were being used, and it looked at endpoints that are basically uninterpretable in a single-arm trial such as progression-free survival and overall survival, as far as regulatory endpoints for us to evaluate the safety or efficacy of this agent.

So although there may be some interesting preclinical data, as well as some hypothesis-generating data that was presented, most of this data would need to be followed up with a much

larger randomized trial in order to determine if this drug is safe and effective. And clearly there are concerns about the safety of this drug, and we don't really have any data to say that it is safe, even in a TNBC or breast cancer population.

So I think from oncology's perspective, we would encourage all of this data be submitted to us for review with a new protocol in order to answer some of these questions that are still outstanding, rather than giving this off label or not under an IND at this point, and I think that's where oncology comes down on it.

Thank you very much. If you have any questions for me, I'm happy to answer them.

DR. VAIDA: Dr. Bormel, do you have a comment?

DR. BORMEL: Yes. Thank you, Dr. Vaida.

I think the nominator posed a question about were there any deaths. It's important to understand that when compounders under Section 503A of the Act -- these are pharmacists and licensed pharmacies, physicians, and federal

facilities -- they have no requirement to report, under Section 503A, adverse events to the agency. So if there are deaths, if there are hospitalizations, we are not necessarily going to hear about that. There is a vehicle for voluntary reporting, but there is no vehicle required under Section 503A to report these adverse events.

I think that's really important to note. When you put a bulk substance on the list, this is going to enable compounders to compound it under 503A -- the pharmacies, the physicians, and the federal facilities -- and there's no mechanism to generate the type of serious adverse event reporting currently under the statute.

DR. VAIDA: Thank you.

I think it's also good to say, too, that 503A compounders do not need to report AEs, whereas outsourcing facilities do.

I would like to state into the record that there are no open public hearing speakers for this topic, and we'll move on to the question to the committee.

The committee will now turn its attention to address --

DR. STEVENSON: Hello, Dr. Vaida. This is Takyiah speaking. I'm sorry to interrupt.

DR. VAIDA: Yes?

DR. STEVENSON: Did you see my note?

DR. VAIDA: Dr. McKinnon has a question or a comment?

DR. McKINNON: Chairman Vaida, Dr. Ganley would like to be recognized for a comment, please.

DR. VAIDA: Fine.

DR. GANLEY: Yes. Hi. This is Charley Ganley. I just wanted to say, in the context of treating cancer, people die from the disease, and the list of diseases that we were asked to review is not just limited to breast cancer.

I am very concerned that this concept that no one's died that was on this therapy, especially in the context of being administered outside of a clinical trial or an IND, I don't know how -- if someone is on the drug, whether it's related to their disease or not, and they die, under an IND,

that would be reported to the agency, and we can make an assessment of whether the drug contributed to that. I suspect there have been many deaths in patients who are being treated for cancer with this drug, and there's just an assumption that it's unrelated to the drug, and we have no evidence of that.

I think the other thing, just to emphasize Dr. Osgood's comments about an IND, it just seems very peculiar that the National Cancer Institute is supporting a phase 2 study presumably to establish that it's safe and effective, yet it can be administered under compounding to patients outside of an IND, and I'm assuming that study's done within the IND framework. That's all my comments. I have no further questions or comments.

DR. VAIDA: Thank you.

DR. OSGOOD: Right. To add to that as well, even in the oncology setting, this will need to be studied at more doses to ensure that you have the optimal dose, as well as to be studied for effectiveness.

I think that based on the data provided, there hasn't been enough dose optimization, as well as safety data collected, on top of efficacy data, and I agree, cancer patients do die, and I would suspect that patients have died while receiving this drug, and we just don't have reports of it, because even if they didn't die from the drug, you would expect a certain number of cancer cases of mesothelioma, colon cancer, and/or breast cancer to have died while receiving this drug.

Committee Discussion and Vote

DR. VAIDA: Thank you.

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 for ammonium tetrathiomolybdate. I'd like to remind the 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. Stevenson will provide instructions for the voting.

DR. STEVENSON: Question 3 is a voting question. Voting members will use the Adobe Connect platform to submit their votes 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: Seeing none, I will hand it back to the chair.

DR. VAIDA: Thank you.

For Section 503A bulk drug substances list, ammonium tetrathiomolybdate, FDA is proposing that ammonium tetrathiomolybdate not be included on the 503A Bulks List. Should ammonium tetrathiomolybdate be placed on the list?

If you vote no, you are recommending FDA not

place the bulk drug substance on the 503A Bulks List. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes subject to an applicable USP or NF monograph component of an FDA drug.

If there are no questions about the wording of the question, we'll now take a vote.

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 2 yeses, 13 noes, and zero abstentions.

(Pause.)

DR. STEVENSON: Sorry, Dr. Vaida. If you are speaking, you may be on mute in Adobe.

DR. VAIDA: Sorry.

We'll now go down the list and have everyone who voted state their name and vote into the record. You can also provide justification for your vote, if you wish to.

I'm Allen Vaida. I voted no because I felt there wasn't enough evidence. There may be some upcoming trials and studies, and this may get revisited in the next couple years.

Dr. Gupta?

DR. GUPTA: Hello. This is Dr. Anita Gupta, and I voted no.

DR. VAIDA: Dr. Serumaga?

DR. SERUMAGA: Yes. Brian Serumaga from USP, and I voted no for the same reasons stated

previously.

DR. VAIDA: Dr. Assis?

DR. ASSIS: David Assis. I voted no for the reasons that were stated. And furthermore, I think this is not a situation in which one needs to lower the safety profile evaluation given that a more stable version of this compound is in the future and can be better evaluated. Thank you.

DR. VAIDA: Dr. Rebello?

DR. REBELLO: This is Elizabeth Rebello. I voted no because I thought the evidence was insufficient.

DR. VAIDA: Dr. Caviness?

DR. CAVINESS: This is John Caviness. I voted yes. My comment is from a movement disorder neurologist perspective, there are patients with Huntington's disease who cannot afford any neurological worsening of their condition, whether that is because of a generalized dystonia or tetering on the edge of being ambulatory or non-ambulatory. So having an alternative treatment that has a much lower risk of worsening is desired,

and hopefully future trials are able to get that done. Thanks.

DR. VAIDA: Dr. Garcia?

DR. GARCIA: Jorge Garcia, University Hospitals, Seidman Cancer Center. I voted no. I think the clinical trials presented today are quite limited, not only in sample size, but certainly the AE profile reports, which appeared to be quite misleading.

In addition to that, the clinical benefit that was observed in the cancer studies to me is pretty minimal, if at all, especially when you have already existing agents now that are part of the standard of care and life prolonging in nature across all those malignancies where this agent was analyzed.

Lastly, the data of the microenvironment is limited and certainly does not explain the mechanism of action, or even can be considered as a predictor of prognostic biomarkers for treatment efficacy with these agents. Thank you.

DR. VAIDA: Dr. Nieva?

DR. NIEVA: I voted no. This is Jorge Nieva. I voted no. ATTM appears to be an effective copper chelator, but like any copper chelator, it can cause copper deficiency, and there are risks that exist whenever any copper chelator is ineffectively monitored.

This agent appears to be at a disadvantage relative to approved drugs for monitoring. The data in cancer are clearly inadequate to justify its use as a cancer therapy outside of a clinical trial, and the fact that its primary use is being presented as a cancer therapeutic is highly concerning.

There may be people who benefit from copper chelation for cancer, but we will never know how to do this correctly in the absence of well-controlled clinical trials. I do not have any sense from this meeting that ATTM is serving any unmet need for patients who cannot tolerate currently available copper chelators. Thank you.

DR. VAIDA: Thank you.

Dr. Gura?

DR. GURA: Hi. Kathleen Gura. I voted yes. Similar to Dr. Caviness, I think there are patients with neurological complications who may benefit, so for that reason I voted yes. Thank you.

DR. VAIDA: Dr. Patel?

DR. PATEL: Hello. This is Kuldip Patel. I voted no for some of the reasons mentioned before and lack of robust and convincing evidence.

DR. VAIDA: Dr. McElhiney?

DR. McELHINEY: This is Linda McElhiney. I voted no because I'm concerned that uninformed practitioners may not monitor their patients as closely as Dr. Rosenberg does.

DR. VAIDA: Dr. Bogner?

DR. BOGNER: Robin Bogner. I voted no, but I look forward to the clinical studies.

DR. VAIDA: Sandra Fusco?

MS. FUSCO-WALKER: Sandra Fusco-Walker. I voted no. The lack of evidence for these compounds is concerning. Informed consent with all the facts when using an unapproved compounded drug is critically important to patients, and I look

forward to the upcoming trials.

DR. VAIDA: Thank you.

Dr. Dasarathy?

DR. DASARATHY: I voted no because I wasn't too convinced about the safety, and I'm also concerned that there is literally no data on the ammonium component, which is really not being studied, and we have spent three decades working on ammonia toxicity in different organs.

DR. VAIDA: Dr. Fensky?

DR. FENSKY: This is Tim Fensky. I voted no for the previous reasons, but especially due to the monitoring parameters that may not be taken into effect. Thank you.

DR. STEVENSON: This is Takyiah Stevenson speaking.

Dr. Dasarathy, could you please state your full name and your vote for the record?

DR. DASARATHY: Oh, I'm sorry. My name is Srinivasan Dasarathy, and I voted no.

DR. STEVENSON: Thank you.

DR. VAIDA: Alright. Thank you, everyone.

Unless there's any concern with the committee, I would like to skip this break and move on to the next topic, and then we could take a short break after that.

Is that ok?

(No audible response.)

DR. VAIDA: Okay.

The next topic is ferric subsulfate. We'll now proceed with the FDA presentation of ferric subsulfate from Dr. Tariq.

DR. TARIQ: Hi. This is Dr. Anam Tariq. Can you hear me ok?

DR. VAIDA: Yes.

DR. TARIQ: Perfect. Thank you.

FDA Presentation – Anam Tariq

DR. TARIQ: Good afternoon. My name is Anam Tariq, and I am from the Pharmacy Compounding Review Team. I will discuss the nomination for ferric subsulfate. I would like to acknowledge the review staff involved in the evaluation of ferric subsulfate, as well as a special thank you to the Division of Urology, Obstetrics, and Gynecology for

their expertise.

Ferric subsulfate, solid or powder, was nominated for inclusion on the list of bulk drug substances for use in the 503A Bulks List. It was proposed for use as an astringent and hemostatic agent during minor surgical procedures for topical routes of administration in the dosage forms of solution and 10 to 21 percent powder.

FDA reviewed publicly available information based on these four criteria. The first criteria is physical and chemical characterization. Ferric subsulfate is also called Monsel's salt and basic ferric sulfate. There is no ferric subsulfate drug substance monograph in the United States Pharmacopeia, British Pharmacopoeia, European Pharmacopoeia, and the National Formulary.

Very limited information was found for ferric subsulfate solid or powder, which we will discuss in this slide. Although ferric subsulfate solid or powder is available directly through several vendors, we found information regarding its use in industrial waste processing as a coagulant

and pigment in pickling baths for steel and aluminum.

It is unclear how ferric subsulfate solid or powder is synthesized, manufactured, isolated, purified, or characterized. Because ferric subsulfate solid or powder is not well characterized physically and chemically, we do not have assurance that its properties and toxicities when used in compounding would be the same as the properties and toxicities reported in the literature and considered by the agency.

Due to the lack of clarity in the nomination and the literature submitted by Fagron regarding whether ferric subsulfate and Monsel's solution or paste refer to a bulk drug substance and a drug product compounded from that substance, respectively, or whether the nominator intended to mean that they are the same products and the names are used interchangeably, FDA interprets the nomination to be for the bulk drug substance ferric subsulfate solid or powder, and data submitted by Fagron on Monsel's will be considered for the

overall assessment and recommendation with respect to the use proposed by the nominator.

Earlier on slide 5, I discussed that there was no ferric subsulfate drug substance monograph, however, please note there is a USP drug product monograph for ferric subsulfate solution, which is also referred to as Monsel's solution. We conclude that there is information available for ferric subsulfate solution, which is Monsel's solution, and it is chemically and physically well characterized when the USP drug product monograph is followed, but the solution is made from ferrous sulfate and not ferric subsulfate solid or powder.

Nonclinical safety data for ferric subsulfate solution, defined as Monsel's solution, was limited to pharmacology studies that investigated the mechanism of action of this substance as an astringent and hemostatic agent. In the rat tail bleeding model, hemostasis was improved when Monsel's solution was used. In the pig model, application of Monsel's solution on punch biopsy sites resulted in the delay of

re-epithelialization on the rate of wound healing. No data were found in the literature that described the acute toxicity, repeat-dose toxicity, reproductive toxicity, genetic toxicology, or carcinogenicity aspects of ferric subsulfate.

Now we will discuss clinical safety. The FDA Adverse Event Reporting System, or FAERS, reported 15 cases of potential drug event associations, with most cases involving application site reactions such as inflammation, pain, irritation, chemical burn, and dysuria.

There were 10 serious adverse events and three cases of compounded products that resulted in hospitalizations, which are shown in the next slide. These three cases were in women with application of Monsel's during intrauterine device procedure or other cervical examination, resulting in hospitalization for burning sensation or other application site burns. Details of the cases were limited on the FAERS database.

A serious adverse event was reported in the literature, where a 46-year-old woman died from

complications of a large cervical biopsy when pads soaked with Monsel's solution were used to control complications of persistent bleeding after unsuccessful hemostasis with suture and other surgical interventions. Based on this serious adverse event, experts recommend that uterine perforation must be excluded before the use of a Monsel's pack because a leak into the peritoneal cavity could lead to areas of bowel damage and necrosis.

On this slide, we will discuss information associated with the use of ferric subsulfate. Monsel's solution may not be an appropriate treatment option for hemostasis during in vitro fertilization because it may inadvertently affect pregnancy outcomes. Pregnancy outcomes were reduced during IVF for the Monsel's group compared to patients in the control group who were undergoing IVF in the same period and did not receive Monsel's solution.

Additionally, ferric subsulfate application causes dyspigmentation at the application site and

may distort pathology on re-excision. This may appear as pathological artifacts and with diagnostic challenges. Histological changes in tissues may persist up to 3 weeks. Experts recommend avoiding cervical smears on patients with recent treatments of ferric subsulfate on the cervix in order to avoid confusion on future diagnosis.

In conclusion, there are no published clinical trials conducted to specifically assess the safety of ferric subsulfate drug products in humans. Adverse events consisted mainly of acute reactions to ferric subsulfate exposure of Monsel's solution or paste.

In literature, ferric subsulfate has been associated with postoperative discharge, delayed wound healing, and vaginal irritation. Although scientific publications in obstetrics and gynecology generally recognize ferric subsulfate as an appropriate hemostatic agent for small amounts of bleeding when applied on the cervical and vaginal epithelium following cervical biopsies and

excisional procedures, Monsel's solution should not be used intra-abdominally because a leak into the peritoneal cavity could lead to areas of bowel damage and necrosis.

Before discussing the effectiveness data for ferric subsulfate, I will spend a few minutes on defining cervical neoplasia and complications of bleeding arising from these diagnostic procedures.

Cervical intraepithelial neoplasia are characterized by atypical squamous changes in the transformation zone of the cervix. Cervical intraepithelial neoplasia are frequently diagnosed and treated among women in reproductive and postmenopausal ages using cervical biopsies with surgical procedures, including cold knife conization, laser conization, and loop electrical excision procedure.

The two most common short-term complications are intraoperative and postoperative bleeding, as well as infection. Intraoperative bleeding is generally controlled using standard surgical techniques with the adjunct use of topical

hemostatic agents, which we will discuss on the next slide.

The American College of Obstetricians and Gynecologists 2020 publication made the following conclusions and recommendations regarding the use of topical hemostatic agents such as ferric subsulfate 20 percent or Monsel's solution. Topical hemostatic agents are not for routine prophylaxis. Topical caustic hemostatic agents such as ferric subsulfate 20 percent or Monsel's solution, aluminum chloride, silver nitrate, and zinc chloride paste are used in the cervix and vagina, but these caustic agents are not for intra-abdominal use.

The agency identified two randomized-controlled trials evaluating the effects of ferric subsulfate drug product on hemostasis predominantly in premenopausal and postmenopausal women undergoing minor surgical procedures on the cervix. In a randomized-controlled trial by Hilal and colleagues, the application of Monsel's solution, defined as ferric subsulfate, was

compared to the control wait-and-see group who did not receive any hemostatic agent or other procedures, which could lead to hemostasis following colposcopy examination for cervical abnormalities.

The primary endpoint was vaginal bleeding after 15 minutes using a scoring sanitary pad with a modified 5-level pictogram and compared between the active treatment and control. The figure on the right shows that Monsel's solution in dark gray experienced less vaginal bleeding. The red arrows on the figure show the reduced vaginal bleeding after the primary endpoint of 15 minutes and secondary endpoints at 3 hours and 6 hours of the procedure. This trial supports efficacy of ferric subsulfate as hemostatic agent in the reduction of vaginal bleeding in the short-term.

In the second controlled trial, Monsel's solution was compared to the control povidone-iodine solution group to investigate postoperative bleeding following LEEP with ball electrode. As shown in the red highlighted box

below, in the Monsel's treated group, the mean, uncomplicated vaginal bleeding, was less than 3 days compared to 5 days in the control group. This article supports the efficacy of ferric subsulfate in reduction of bleeding following LEEP.

This slide describes the articles submitted by the nominator. We evaluated these studies, however, in conclusion, these studies did not have adequate controls or it was not possible to estimate the contribution of ferric subsulfate solution towards hemostasis as opposed to other factors.

Overall, we conclude there is evidence of effectiveness for the use of ferric subsulfate as a topical hemostatic agent, based on data from randomized-controlled trials to reduce bleeding following minor gynecological surgical procedures that include cervical biopsies.

Lastly, we apply the fourth criteria that is the historical use. We do not have information on the extent to which the products are compounded starting from ferric subsulfate solid or powder.

Results using the term "ferric subsulfate compounding pharmacy" indicate that ferric subsulfate is commonly compounded as a topical solution and gel for hemostasis. Additionally, the active ingredient is found in certain unapproved prescription and non-prescription products marketed in the United States for human and animal use for hemostasis.

Based on this information, we have considered a balancing of the four evaluation criteria that weighs against ferric subsulfate solid or powder being added to the 503A Bulks List, primarily because of the lack of information on the physical and chemical characterization of ferric subsulfate solid or powder. Thank you very much. That concludes my presentation.

Clarifying Questions from the Committee

DR. VAIDA: Thank you.

We will now take clarifying questions for the 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 end of your follow-up questions with, "That is all for my questions," so we can move on to the next panel member.

Dr. McElhiney?

DR. McELHINEY: This is Linda McElhiney

DR. VAIDA: Sorry.

DR. McELHINEY: That's ok. This is Linda McElhiney. This is for Dr. Tariq.

Just to clarify, this is only for the bulk powder. It's not for the commercial Monsel's solution that's already available commercially through several manufacturers, and has a USP monograph. Thank you.

DR. TARIQ: Thank you for the question.

Yes, we evaluated the ferric subsulfate solid or powder for this specific evaluation, and I will let my colleagues in OCQC add context regarding the interpretation of the nomination.

DR. LAWSON: Hi. This is Rosilend Lawson from OCQC. FDA is aware of the wide use of Monsel's solution prepared according to the USP drug product monograph, and we are exploring options to clarify its policy with respect to distribution of this product.

Did that answer your question?

DR. McELHINEY: Yes.

DR. VAIDA: Dr. Eisenberg?

DR. EISENBERG: Yes. This is Dr. David Eisenberg, an OB/GYN at Washington University School of Medicine in St. Louis. I have a couple questions about this distinction between compounded ferric sulfate versus the FDA-approved marketed ferric subsulfate solution that's available, like you said, through the USP process.

Number one is with regards to adverse events. If someone will pull up either slide 14, I

believe it was, with regards to the FAERS database; this was specific to reported adverse events with the compound -- I guess it was slide 11. There you go. Slide 11 was specific to -- can you advance one more? There you go. These three were specific to compounded ferric subsulfate; is that correct? Thank you.

DR. TARIQ: Hi. This is Anam Tariq. Thank you for the question. Yes, for these three cases that we showed here on this slide, specifically it was related to compounded products that contained ferric subsulfate.

DR. EISENBERG: And some follow-on questions -- and I am aware of this case report of ferric subsulfate in the peritoneal cavity as a result of unrecognized vaginal colpotomy occurring at the time of a large LEEP procedure.

Do we know if that and/or any of the other reports that were in the FAERS database -- I believe there were 15 cases altogether as displayed on slide 14 -- were those related to the FDA-approved ferric subsulfate or compounded ferric

subsulfate?

DR. TARIQ: Hi. This is Anam Tariq again. There is no FDA-approved medication that contains ferric subsulfate. As I pointed earlier in the slide, there is a USP drug product monograph that has the recipe how to make ferric subsulfate solution, which, as you referred to earlier, was used in the patients, three of which were compounded products that mentioned that they were adverse events.

But again, because of the FAERS database, we are not able to elucidate how and where the actual active ingredient was made or produced. and neither of the cases reported sufficient information to establish causality, but the specific case that you mentioned of the peritoneal perforation -- I'm sorry. What was the second part of the question for the peritoneal perforation?

DR. EISENBERG: Specifically, could we state as to whether it was the USP-approved monograph production or not? As a clinician, I'm not sure I understand the distinction between the USP-approved

monograph, of the creation of Monsel's solution versus the FDA approval process, versus the question at hand, which is with regards to whether ferric subsulfate should be listed on the bulk compounding list.

I'm just trying to understand the adverse event rate or the number of adverse event reports for the USP-approved ferric subsulfate.

DR. KASIM: Dr. Tariq?

DR. TARIQ: Yes?

DR. KASIM: This is Suhail Kasim, lead physician in the Office of New Drugs in pharmacy compounding. Do you mind if I respond, Dr. Tariq?

DR. TARIQ: Yes. Please go ahead, Dr. Kasim.

DR. KASIM: Dr. Eisenberg, I think I understand your question. You're trying to elucidate whether we have information about whether we can say the adverse events were due from the products that were compounded based on the USP drug product monograph or from other ways of compounding use.

To answer that, we don't know. As Dr. Tariq said, we don't know. I think we tried to acknowledge that in the evaluation. The assumption is made that most of the data that we have evaluated for safety, or for effectiveness, were based on what was available and reported in the literature. The literature report called it at Monsel's or ferric subsulfate, and the USP product monograph has a certain percentage of concentration associated with that ferric subsulfate that is compounded.

Now, that is the limitation of the information we have. But the FAERS database, I think, for these three cases may have called out that it was based on Monsel's paste or Monsel's solution. So with that assumption, Monsel's may be that USP drug product monograph. I hope that answers your question.

DR. EISENBERG: Yes. That is helpful. You're exactly right, that I was just trying to understand is there a different safety profile for this idea of compounded versus the USP-approved

production, and it sounds like the answer is we don't know.

DR. KASIM: We don't know.

DR. EISENBERG: The next question I have is whether the FDA in reviewing this had any concerns about the very common widespread usage of the USP-approved Monsel's solution? Because we don't have well-controlled studies regarding safety and efficacy, and this product, as mentioned, has been around since Napoleon's army.

So it's just hard to say that it is the compounded product that is more concerning when it may just simply be that inadequate or inappropriate use, I should say, of this medication can obviously result in adverse events. Thank you for the clarifications.

DR. LAWSON: This is Rosilend Lawson again. The USP drug product monograph for ferric subsulfate solution describes the procedure that starts with ferrous sulfate to prepare the ferric subsulfate solution. Ferric subsulfate solution is chemically and physically well characterized when

the USP drug product monograph is followed, but this solution that's being made from the powder or the solid, which we construe to be the subject of the nomination, is not well characterized, and that's why we recommended that it not be placed on the bulks list.

Having said that, we recognize this unusual issue that's presented today and the wide use of Monsel's solution prepared according to the drug product monograph, and we intend to explore options to clarify our policy on making that later with respect to distributing the product.

DR. BORMEL: Yes. This is Gail Bormel. There are a couple layers to your question, and what my colleagues have said is absolutely correct. What we're dealing with now is ferric subsulfate as a solid or powder being placed on the bulks list, and that's separate from the USP drug product finished dosage form monograph of Monsel's solution. There is no FDA-approved drug product of Monsel's solution, just to be clear, so any data we're getting on Monsel's solution reported is

going to be voluntary data reported through the FAERS system.

The data are what the data are. The Monsel's solution has been made for a long time, and the fact that there's a USP monograph means there are certain standards to how you make it and what it's supposed to come out to be, and that is in the USP. And by what we're doing now, we're not addressing that Monsel product solution. What we're dealing with is the placement of a bulk powder or bulk solid on the 503A list of ferric subsulfate.

I'll just mention that the USP drug product monograph of Monsel's solution starts with a different compound to make it. It starts with ferrous sulfate. So we are not opining on that Monsel's solution today; we're only dealing with what we've talked about so far, which is the powder of ferrous sulfate, or solid form.

Is that a little more clear?

DR. EISENBERG: Yes. I very much appreciate the clarification. It is an unusual situation that

we find ourselves in, and I do want to make sure that we are not somehow criticizing or, like you said, espousing on the utility or safety of the USP monograph, and it really is just confined to this question of the bulk product on the solid form. Thank you for the clarifications, for everyone.

DR. BORMEL: Right. And if you notice, it has a lot to do with the lack of ability to characterize the ferric subsulfate substance itself. You restated it perfectly, so I think you do understand. Thank you.

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

DR. BOGNER: I just wanted to make a comment that I don't think that the ferric subsulfate is very well characterized. I looked it up in various places, and in some places it's described as yellow; other places it's reddish brown; and other places it's yellowish-brown. Whether this is due to a difference in composition or particle size is possible, but I suspect that it's just not well characterized as a solid.

In addition, one compounding supplier lists the formula as an approximate formula, meaning that I'm not sure it's well characterized there either. Thirdly, I was really surprised that there is no pH test for Monsel's solution. It seems that that would be pretty important. I don't think people are making Monsel's solution from ferric subsulfate -- sorry, the ferrous, only because it has to be heated until red fumes cease to be evolved, and I doubt very many people are doing that in pharmacies.

If anybody has a comment on a different understanding than mine -- in other words, is it better characterized -- I would like to hear that. Thank you.

DR. VAIDA: Alright.

Dr. McElhiney, do you have a follow-up?

DR. McELHINEY: This is Linda McElhiney. I've got a comment. I'm a compounder. I compound for a large health system, and we've never compounded Monsel's from the solid powder. We've always bought the commercial --

DR. BOGNER: Right. Exactly.

DR. McELHINEY: -- product from the chemical wholesalers, and it's always the USP grade. So I don't think -- I've never heard of anybody compounding it. And probably another reason they don't do it is because they're following the USP monograph, and they should be using a ferrous sulfate. That might be a completely different concentration than using the straight ferric subsulfate powder, and might end up being a lot more caustic or maybe stronger than using the ferrous sulfate.

So I don't think that it's even necessary. There are so many manufacturers that commercially produce the Monsel's USP product. Thank you.

Committee Discussion and Vote

DR. VAIDA: Thank you.

I would like to state into the record that we do not have a nominator presentation for this topic. I would also like to state into the record that there are no open public hearing speakers for this topic.

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 [inaudible – audio gap]. We will proceed with the questions to the committee. 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. Stevenson will provide the instructions for the voting.

DR. STEVENSON: Question 4 is a voting question. Voting members will use the Adobe Connect platform to submit their votes 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: Seeing none, I will give it back to the chair to read the question.

DR. VAIDA: Thank you.

Question number 4, for the Section 503A bulk drug substances list, ferric subsulfate, FDA is proposing that ferric subsulfate solid or powder not be included on the 503A Bulks List. Should ferric subsulfate solid or powder be placed on the list?

If you vote no, you are recommending FDA not place the bulk drug substance on the 503A Bulks List. If the substance is not on the list when the final rule is promulgated, compounders may not use the drug for compounding under Section 503A unless it becomes the subject of an applicable USP or NF monograph, or a component of an FDA-approved drug.

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

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.)

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 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 want to.

There are zero yeses, 12 noes, and zero abstentions.

DR. VAIDA: Okay. Thank you

As stated, I'll now go down the list and have everyone who voted state their name and vote, and you could also provide justification, if you wish to.

I'm Allen Vaida, and I voted no.

Dr. Gupta?

DR GUPTA: Hi. I'm Anita Gupta, and I voted no.

DR. VAIDA: Dr. Serumaga?

DR. SERUMAGA: Hi. I'm Brian Serumaga, and I voted no because whereas USP has a drug product monograph for ferrous subsulfate solution, the information that would be required to characterize the ferric subsulfate drug bulk substance cannot actually be deduced from this monograph. So I wasn't reassured by any of the evidence provided today that this chemical can actually be characterized.

Also, inferring, through the databases that are frequently used by compounders to source the ingredients using compounding, there is sufficient evidence that ferric subsulfate solution, which conforms to the drug product monograph of ferric subsulfate solution is actually readily available to compounders. So for those reasons, I voted no.

DR. VAIDA: Thank you.

Dr. Eisenberg?

DR. EISENBERG: Yes. This is Dr. David Eisenberg. I also voted no and in agreement with many of the conclusions the FDA made, specifically that there is a USP available monograph for ferric subsulfate solution that's widely available, and that there's no need for this difficult to characterize product in bulk form to be available.

DR. VAIDA: Dr. Rebello?

DR. REBELLO: This is Elizabeth Rebello. I also voted no for the reasons that were stated previously.

DR. VAIDA: Thank you.

Dr. Gura?

DR. GURA: Hi. This is Kathleen Gura. I voted no for the same reasons.

DR. VAIDA: Dr. McElhiney?

DR. McELHINEY: Linda McElhiney. No.

DR. VAIDA: Dr. Lindsay?

DR. LINDSAY: Michael Lindsay. I voted no for the reasons that have already been mentioned.

DR. VAIDA: Dr. Bogner?

DR. BOGNER: Robin Bogner. I voted no.

DR. VAIDA: Sandra Fusco-Walker?

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

DR. VAIDA: Thank you.

It looks like the committee overwhelmingly voted no on this topic for many of the reasons that were discussed.

DR. STEVENSON: I'm so sorry to interrupt, Dr. Vaida. This is Takyiah speaking. I do not believe we heard from Dr. Patel or Dr. Fensky, with their name and vote.

DR. VAIDA: Dr. Patel?

DR. PATEL: Hi. Kuldip Patel, and I voted no. Thank you.

DR. VAIDA: Dr. Fensky?

DR. FENSKY: Timothy Fensky, and I voted no.

DR. VAIDA: Thank you.

Thank you, everyone. We'll now take a 10-minute break and reconvene at 4:30. Thank you.

(Whereupon, at 4:19 p.m., a recess was taken.)

DR. VAIDA: I now would like to welcome

everyone back, and we'll have Dr. Stevenson read the Conflict of Interest Statement for this meeting's Withdrawn or Removed List topic.

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

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

and to the public.

FDA has determined that members and temporary voting members of this committee are in compliance with federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts when it is determined that the agency's need for a special government employee's services outweighs 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 the 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 the revisions FDA is considering for the Withdrawn or Removed List. FDA is now considering whether to amend the rule to add one more entry to the list, lorcaserin hydrochloride: all drug products containing lorcaserin hydrochloride.

As previously explained in the Federal Register of July 2, 2014, 79 FR 37687 at 37689 through 37690, the list may specify that a drug may not be compounded in any form, or alternatively may expressly exclude a particular formulation, indication, dosage form, or route of administration from an entry on the list.

Moreover, a drug may be listed only with regard to certain formulations, indications, routes of administration, or dosage forms because it has been found to be unsafe or not effective in those particular formulations, indications, routes of

administration, or dosage forms. FDA plans to seek the committee's advice concerning the inclusion of this drug on the list.

This is a particular matters meeting during which specific matters related to lorcaserin hydrochloride will be discussed. Based on the agenda for this meeting and all financial interest reported by the committee members and temporary voting members, a conflict of interest waiver has been issued in accordance with 18 U.S.C. Section 208(b)(3) to Dr. Kathleen Gura. Dr. Gura's waiver involves stock holdings of an affected entity. The aggregate value of the stock is between $50,000 and $100,000.

The waiver allows the individual 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 waiver 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 committee members and temporary voting members to disclose any public statements that they have made concerning the topic 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 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 topics that are 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 topic at issue.

Thank you. I will turn it back to the chair.

DR. VAIDA: Thank you, Dr. Stevenson.

We'll now proceed with FDA's presentation on the Withdrawn or Removed List process from Gabrielle Cosel.

FDA Presentation – Gabrielle Cosel

MS. COSEL: Thank you very much, and good afternoon. My name is Gabrielle Cosel, and I'll be providing a brief overview of FDA's process for creating the Withdrawn or Removed List.

One of the conditions that must be satisfied for a drug product to qualify for the exemptions under Section 503A or 503B of the Food, Drug, and Cosmetic Act is that the compounder does not compound a drug product that appears on a list of products that have been withdrawn or removed from the market due to reasons of safety or effectiveness, and we call this the Withdrawn or

Removed List.

FDA has reviewed and added 85 bulk drug substances to the Withdrawn or Removed List to date. The way that we approach maintaining this list is that we periodically review available information on drugs that are withdrawn or removed from the market due to reasons of safety or effectiveness with the goal of identifying possible new entries.

The information we review may include Federal Register notices announcing withdrawal of approval of a new drug application, or abbreviated new drug application, for safety or effectiveness reasons, or Federal Register notices announcing an agency determination that a drug product that was voluntarily withdrawn from sale was withdrawn for reasons of safety or effectiveness.

We also review available information to determine whether any approvals of new drug applications would warrant modifications to existing entries on the list. Appropriate divisions within our Office of New Drugs evaluate

each identified candidate or proposed modification using available information about the drug. The responsible division will prepare a review of that information to document its recommendations.

FDA will update the Withdrawn or Removed List through notice and comment rulemaking, as we clarified in the final rule in 2016. We intend to propose regulations to revise the list when we identify drugs that we tentatively determine should be listed, and we also intend to propose regulations when we determine that changes to the status of drugs already on the list should be revised.

Generally, we will finalize any additions or modifications to the list after we consult the advisory committee about the product and after providing an opportunity for public comments to be submitted on a proposed rule.

Today we'll be discussing one substance that FDA is considering including on the list, and that is lorcaserin hydrochloride: all drug products containing lorcaserin hydrochloride. And with

that, I'll turn it back to the chair.

DR. VAIDA: Thank you.

We'll now proceed with the FDA presentation on lorcaserin hydrochloride from Dr. Marianne San Antonio.

FDA Presentation – Marianne San Antonio

DR. SAN ANTONIO: Hi. Good afternoon. My name is Marianne San Antonio, and I am a physician in the Office of New Drugs. I will discuss the nomination for lorcaserin hydrochloride for possible inclusion on the Withdrawn or Removed List. I would like to recognize the entire evaluation team, as well as the contribution of many other FDA colleagues who helped with this evaluation, special thanks to the Division of Diabetes, Lipid Disorders, and Obesity.

The Withdrawn or Removed List is a list of drug products that were withdrawn or removed from the market because the products were found to be unsafe or not effective. Drugs on the list cannot qualify for exemptions under Section 503A or 503B, and cannot be compounded.

Lorcaserin hydrochloride, whose trade name was Belviq, is a selective agonist of the 5-hydroxytryptamine, or 5-HT, 2C receptors. It was available in 10-milligram immediate-release or 20-milligram extended-release oral tablets. These formulations were approved on June 27, 2012 and July 15 2016. The approval for NDA 022529 included a postmarketing requirement for a study investigating cardiovascular adverse events associated with the use of lorcaserin hydrochloride. It was indicated for use as an adjunct to a reduced-calorie diet and increased physical activity for the treatment of chronic weight management in adults with either obesity or overweight, and at least one other weight-related comorbid condition.

The postmarketing study, CAMELLIA-TIMI 61, which stands for cardiovascular and metabolic effects of lorcaserin in overweight and obese patients, thrombolysis, and myocardial infarction, was conducted by the sponsor to investigate cardiovascular adverse events associated with the

use of lorcaserin hydrochloride. Safety concerns were identified, but rather than cardiovascular safety concerns, the primary safety concern was a possible increased risk of malignancy. Subsequently, lorcaserin hydrochloride drug products were withdrawn from the market for safety reasons.

Next, we will discuss the postmarketing safety data that led to this withdrawal, and then we will review lorcaserin hydrochloride's regulatory history.

A postmarketing safety study was required by FDA at the time of lorcaserin hydrochloride's approval because of the occurrence of cardiovascular adverse events during treatment with other FDA-approved medications for weight loss. Those medications had similar mechanisms of action to lorcaserin hydrochloride and were previously withdrawn from the market.

The trial included 12,000 overweight or obese adult subjects with or at high risk for atherosclerotic vascular disease. The primary

endpoints were risks for pulmonary hypertension and valvular heart defects associated with lorcaserin hydrochloride treatment. In the trial, neither pulmonary hypertension nor valvular heart defects occurred at an increased rate in patients treated with lorcaserin hydrochloride compared to placebo.

The FDA's analysis of the study data suggested an imbalance in cancer in humans with an increased risk of malignancy when oral lorcaserin hydrochloride was used for chronic weight management in adults. Rates of certain cancers were higher in the lorcaserin hydrochloride group. These included colorectal cancer, pancreatic cancer, and lung cancer.

Within the first 180 days of treatment, the number of patients with a new cancer diagnosis was similar in the lorcaserin hydrochloride and placebo groups. However, beyond 180 days of treatment, cancer risk was elevated among patients in the lorcaserin hydrochloride group.

It is unclear by what mechanism lorcaserin hydrochloride is associated with cancer. However,

the signal persisted through multiple analyses, and the clinical findings were corroborated by the evidence from animal models. Additional evidence would be necessary to investigate the signal, but FDA determined that it is unlikely that the necessary safety endpoints such as cancer can be readily or ethically investigated in a clinical trial.

In 2012, the approval for lorcaserin hydrochloride 10-milligram tablets under NDA 022529 included a postmarketing requirement to evaluate the risk of cardiovascular adverse events associated with the use of lorcaserin hydrochloride. The CAMELLIA-TIMI study has fulfilled this requirement, and data was collected from 2014 to 2018. Although the primary outcome measure of the study was to evaluate the risk of cardiovascular problems associated with the use of lorcaserin hydrochloride, FDA's analysis of the results suggested an imbalance in cancer in humans.

In a drug safety communication issued on January 14, 2020, the FDA alerted the public that

study results showed a possible increased risk of cancer associated with lorcaserin hydrochloride. In a drug safety communication issued on February 13, 2020, the FDA asked the sponsor to voluntarily withdraw lorcaserin hydrochloride from the U.S. market. The sponsor requested FDA to withdraw approval of the NDAs for Belviq and Belviq XR.

On September 17, 2020, FDA published a Federal Register notice withdrawing approval of the applications for lorcaserin hydrochloride 10-milligram tablets and 20-milligram extended-release tablets. On March 4, 2021, FDA published a notice in the Federal Register announcing that Belviq 10-milligram tablets and Belviq XR 20-milligram tablets were withdrawn from sale for reasons of safety or effectiveness, and both products were removed from the Orange Book.

In summary, data from the CAMELLIA-TIMI 61 clinical study and nonclinical data suggest an increased risk of malignancy with use of lorcaserin hydrochloride. FDA concluded that lorcaserin

hydrochloride's benefits do not outweigh the risks for the current indications. We are not aware of data suggesting that the increased risk of malignancy is restricted to particular lorcaserin hydrochloride drug products, and lorcaserin hydrochloride was withdrawn from the market due to safety concerns.

FDA recommends that all drug products containing lorcaserin hydrochloride be included on the Withdrawn or Removed List using the following entry: lorcaserin hydrochloride: all drug products containing lorcaserin hydrochloride. Thank you. This concludes my presentation.

DR. VAIDA: Thank you.

We'll 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 question," so we can move on to the next panel member.

(Pause.)

DR. VAIDA: I do not see any raised hands currently. Are there any questions from the panel?

(No response.)

Open Public Hearing

DR. VAIDA: Since there are no questions, we will now begin the open public hearing session.

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

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of

your written or oral statement to advise the committee of any financial relationships that you may have with the product and if known, its direct competitors.

For example, this financial information may include the payment for 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 for your cooperation.

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

DR. CAROME: Good afternoon. I'm Dr. Michael Carome, director of Public Citizen's Health Research Group. I have no conflicts of interest.

Slide 2. Public Citizen urges the Pharmacy Compounding Advisory Committee to endorse the FDA's proposal to add all drug products containing lorcaserin hydrochloride to the list of drug products that have been withdrawn or removed from the market because they have been found to be unsafe or not effective, and that therefore may not be compounded under the exemptions provided under

Section 503A and Section 503B of the Food, Drug, and Cosmetic Act; hereafter, the Withdrawn or Removed List codified at 21 CFR, Section 216.24.

Slide 3. The correct vote on this matter could not be more obvious. On March 4, 2021, the FDA published a notice in the Federal Register announcing that the agency had determined that Belviq lorcaserin hydrochloride tablets 10 milligrams and Belviq XR lorcaserin extended-release tablets 20 milligrams, which were initially approved by the FDA in June 2012 and July 2016, respectively, as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in certain adults who are overweight or obese, were withdrawn from sale for reasons of safety or effectiveness, and that the agency would not accept or approve abbreviated new drug applications, or ANDAs, for lorcaserin hydrochloride tablets 10 milligrams and 20 milligrams.

Slide 4. The following excerpts from the FDA's March 4, 2021 notice indicate that these

lorcaserin products were withdrawn from sale specifically for reasons of safety.

Quote, "In 2012, the agency required the drug manufacturer to conduct a randomized, double-blind, placebo-controlled trial to evaluate the risk of cardiovascular problems. The CAMELLIA-TIMI 61 clinical trial was conducted to fulfill this requirement. An analysis of the CAMELLIA-TIMI 61 trial results suggests an imbalance in cancer in humans. Although chance effects cannot be ruled out, the imbalance persisted through multiple analysis approaches.

"The clinical findings corroborated by the evidence from animal models informed the agency's assessment that the risk outweighs any potential benefits for current indications. These findings were considered clinically meaningful and could not be adequately addressed through labeling.

"Additional evidence would be necessary to investigate the signal. However, the agency has determined that it is unlikely that the necessary safety endpoints, i.e., cancer and reproductive

safety, can be readily or ethically investigated in a clinical trial. Because preclinical or clinical studies would first need to be conducted to address these concerns, the agency has determined that this drug would not be considered safe and effective if it were reintroduced into the market.

"The FDA issued a drug safety communication on January 14, 2020, alerting the public that results from a clinical trial assessing the risk of heart-related problems show a possible increased risk of cancer with Belviq and Belviq XR.

"On February 13, 2020, FDA announced that it had asked Eisai to voluntarily withdraw Belviq and Belviq XR from the U.S. market. On February 13, 2020, Eisai submitted a request to FDA to withdraw approval of the NDA for Belviq and Belviq XR under 21 CFR 314.150(d) and waived its opportunity for a hearing. As requested by Eisai, the agency issued a Federal Register notice on September 17, 2020, withdrawing approval of the application for Belviq tablets 10 milligrams and Belviq XR 20 milligrams, effective September 17, 2020.

"Accordingly, the agency will remove Belviq lorcaserin hydrochloride tablets 10 milligrams and Belviq XR lorcaserin hydrochloride extended-release tablets 20 milligrams from the list of products published in the Orange Book. FDA will not accept or approve ANDAs that refer to this drug product," end quote.

Slide 5. Importantly, the Pharmacy Compounding Review Team from the Center for Drug Evaluation and Research's Office of New Drugs appropriately recommended that all drugs containing lorcaserin hydrochloride be included on the Withdrawn or Removed List.

In support of this recommendation, the OND observed the following: 1) lorcaserin products were withdrawn from the market for safety reasons with the primary safety concern being the drug's increased risk of malignancy that was observed in both the postmarketing trial data from the CAMELLIA-TIMI 61 trial and nonclinical studies; and 2) although the mechanism by which lorcaserin hydrochloride is associated with malignancy is

unknown, OND is not aware of data or information suggesting that the increased risk of malignancy is restricted to particular drug products containing the active pharmaceutical ingredient lorcaserin hydrochloride.

Slide 6, my final slide. Public Citizen therefore urges you to protect public health by voting in favor of the FDA's proposal that, quote, "lorcaserin hydrochloride: all drug products containing lorcaserin hydrochloride," be added to the Withdrawn or Removed List under Section 503A and 503B of the Food, Drug, and Cosmetic Act.

Moreover, moving forward, the FDA should not delay initiating the notice and comment rulemaking process for amending FDA regulations at 21 CFR Section 216.24 once the agency has published a determination that a drug product was withdrawn from sale for reasons of safety.

Instead, to better protect public health, whenever the FDA issues a notice announcing such a determination, the agency simultaneously should issue a notice of proposed rulemaking, proposing to

amend the Withdrawn or Removed List under FDA regulations at 21 CFR, Section 216.24 to include that drug product. Thank you for your attention.

DR. VAIDA: Thank you.

Our next speaker, your audio is connected now. Will speaker number 2 begin and introduce yourself? State your name and any organization you are representing for the record.

DR. ZELDES: Good afternoon. Thank you for the opportunity to speak today on behalf of the National Center for Health Research. I am Dr. Nina Zeldes, a senior [inaudible – audio gap] at the center. We analyze scientific data to provide objective health information to patients, health professionals, and policymakers. We do not accept funding from drug or medical device companies, so I have no conflict of interest.

In this session, the committee is asked to vote whether you agree with FDA's proposal that drug products containing lorcaserin hydrochloride should be added to the Withdrawn or Removed List. Since this list includes drugs that were withdrawn

or removed from the market because they've been found to be unsafe or ineffective, and because Belviq has been withdrawn from the U.S. market for safety reasons, there is no reason why this product should still be available for compounding. In fact, it has long been clear that Belviq poses a risk to patients.

FDA already alerted the public more than two years ago, in January 2020, that the results from a postmarketing study which evaluated the risk of cardiovascular problems showed an increased risk of cancer. As a result, FDA asked the drug manufacturer to withdraw this drug from the U.S. market one month later. This trial showed that compared to placebo, patients taking lorcaserin had more total cancers, more cancer deaths, more patients with multiple primary treatments, and more patients with metastatic disease.

Even in the observed excess [indiscernible], cancer risk was small, FDA announced that the risks of Belviq outweigh any potential benefit and withdrew the drug from sale for reasons of safety

or effectiveness in March 2021, and yet this drug has not been added to the Withdrawn or Removed List. Delaying the inclusion of unsafe drug products poses an entirely avoidable risk to patients. This is unacceptable.

Unfortunately, this is not the first time that drug products that were deemed unsafe were not added to this list in a timely fashion. When the Withdrawn or Removed List was established in 1999, it included 59 drug products and has been updated only twice since then, once in 2016 to include an additional 24 products, and one in 2018 to add another two drug products.

These added drugs have in most cases already been withdrawn or removed from the market over concerns of safety or effectiveness several years before. According to Section 503A of the federal Food, Drug, and Cosmetic Act, FDA shall convene and consult an advisory committee on compounding, as it has today, and it also allows the issues of such regulations before consultation if the secretary determines that this is necessary to protect the

public health.

For many of these drugs, including Belviq, we argue that an inclusion on the list at the same time as the product is withdrawn from the market is necessary to protect the public health. In addition to adding Belviq to the Withdrawn or Removed List as soon as possible, we agree with Public Citizen's 2021 petition that the current regulations should be revised so that every time a drug product is withdrawn or removed from market over safety or effectiveness concerns, that product will also be included on this list at the same time.

Such an amendment will reduce the time potentially harmful drugs continue to be available for compounding and will help eliminate this entirely unnecessary risk for patients. Thank you for your time.

Committee Discussion and Vote

DR. VAIDA: Thank you.

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 public comments. We will proceed with the question to the committee. 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. Stevenson will provide the instructions for the voting.

DR. STEVENSON: Question 5 is a voting question. Voting members will use the Adobe Connect platform to submit their votes 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: Seeing none, I will turn it back over to the chair.

DR. VAIDA: Thank you .

Question number 5 is drugs to be considered for the Withdrawn or Removed List, lorcaserin hydrochloride. The vote is FDA is proposing that lorcaserin hydrochloride, all drugs containing lorcaserin hydrochloride, be added to the Withdrawn or Removed List under Sections 503A and 503B of the Food, Drug, and Cosmetic Act. Do you agree?

Does the committee have any questions on the wording, since the wording on this is a little different with what a no or a yes means? Are there any questions or comments concerning the wording?

(No response.)

DR. STEVENSON: Alright. Seeing none, 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 is closed and is

now complete. Once the vote results display, I will read the vote results 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 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 want to.

There are 10 yeses, zero noes, zero abstentions.

(Pause.)

DR. STEVENSON: Dr. Vaida, if you are speaking, I do see that you are on mute.

DR. VAIDA: Sorry. Sorry about that.

Thank you. We will now go down the list and have everyone who voted state their name and vote into the record, and as stated, if you want to provide justification for your vote, if you wish.

I'm Allen Vaida. I voted yes, and I think our two open public speakers eloquently gave

reasons why I voted yes.

Dr. Gupta?

DR. GUPTA: I'm Anita Gupta, and I voted yes, and I agree. I believe that there are strong reasons to place this product on the Withdrawn or Removed List. Thank you.

DR. VAIDA: Dr. Serumaga?

DR. SERUMAGA: It's Brian Serumaga, and I voted yes.

DR. VAIDA: Dr. Rebello?

DR. REBELLO: This is Elizabeth Rebello, and I also voted yes.

DR. VAIDA: Dr. Gura?

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

DR. VAIDA: Dr. Patel?

DR. PATEL: Hi. This is Kuldip Patel, and I voted yes. Thank you.

DR. VAIDA: Dr. McElhiney?

DR. McELHINEY: Linda McElhiney, and I vote yes.

DR. VAIDA: Dr. Bogner?

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

DR. VAIDA: Sandra Fusco-Walker?

MS. FUSCO-WALKER: Sandra Fusco-Walker, and I voted yes.

DR. VAIDA: And Dr. Fensky?

DR. FENSKY: This is Timothy Fensky, and I voted yes. Thank you.

DR. VAIDA: Thank you, everyone.

It looks like we overwhelmingly voted yes for this. I would just like to make one other comment, that I've been on this committee before, and I've heard the comments before on more timely adding to the Withdrawn or Removed List, and I agree with both of the open public speakers.

Before we adjourn, are there any last comments from the FDA?

DR. GANLEY: Hi. This is Charley Ganley. I just wanted to thank all the committee members for their time today, and thank you for a great meeting. Thanks.

Adjournment

DR. VAIDA: Alright. Thank you.

I also would like to thank all the committee and panel members, and the FDA, for what turned out to be a long day, but everyone hung in there, and it looks like we got back on time.

So thank you, everyone, and we will now adjourn the meeting.

(Whereupon, at 5:12 p.m., the afternoon session was adjourned.)