FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACY COMPOUNDING ADVISORY COMMITTEE (PCAC)

Afternoon Session

Virtual Meeting

Wednesday, June 9, 2021

3:05 p.m. to 6:09 p.m.

Meeting Roster

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C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

(3:05 p.m.)

DR. GULUR: Welcome back, everybody. Before we begin, Dr. Takyiah Stevenson will introduce the new special government employees, industry representative, and FDA presenters for the afternoon topics.

DR. STEVENSON: Hello. This is Takyiah Stevenson again.

Dr. Jennifer Lai, please state your name and your affiliation for the record.

DR. LAI: Yes. Hi. My name is Jennifer Lai. I'm a hepatologist at UC San Francisco and director of hepatology clinical research for UCSF health. Thank you.

DR. STEVENSON: Dr. Liangpunsakul?

DR. LIANGPUNSAKUL: Hi. My name is Dr. Suthat Liangpunsakul, professor of medicine at the Indiana University School of Medicine in Indianapolis.

DR. STEVENSON: Dr. Bassani?

DR. BASSANI: Yes. Good afternoon. I'm Gus Bassani. I serve as chief scientific officer for PCCA in Houston, Texas.

DR. STEVENSON: I will now introduce the FDA participants.

Dr. Wolfert?

DR. WOLFERT: Yes. Thank you. I'm Madeline Wolfert. I'm a physician with the Pharmacy Compounding Review Team with the Office of New Drugs, FDA.

DR. STEVENSON: Dr. Hong?

(No response.)

DR. STEVENSON: Dr. Hong, if you can hear me, please unmute and introduce yourself.

DR. HONG: Sure. Hi. I'm sorry. I was double-muted. This is Jay Ho Hong. I'm with the Division of Anti-Infectives, and I'm a medical officer. Thank you.

DR. STEVENSON: Thank you so much.

I will hand it back to the chair, Dr. Gulur. Thank you.

DR. GULUR: Thank you, Takyiah.

We will now proceed with the FDA presentation on choline chloride for Dr. Suhail Kasim.

FDA Presentation – Suhail Kasim

DR. KASIM: Good afternoon. I'm Suhail Kasim

from the Office of New Drugs. I will discuss the nomination for choline chloride. This slide shows the review staff involved in the choline chloride evaluation.

Choline chloride was proposed for use with respect to liver diseases, including non-alcoholic fatty liver disease, hepatic steatosis, fetal alcohol spectrum disorder, and atherosclerosis. In addition to these uses, this evaluation considers the use of choline chloride for supplementation in long-term total parenteral nutrition.

Choline chloride has been nominated and proposed for use to be administered by the parenteral injection route. In conducting the 503A evaluation, FDA reviewed publicly available information to assess choline chloride based on four criteria.

The first criteria applied was the information considered regarding the physical and chemical characterization of choline chloride. Choline chloride is well characterized physically and chemically and is likely to be stable under ordinary storage conditions in the proposed dosage form. I will discuss briefly the

general pharmacology of choline.

Choline chloride is an essential nutrient existing in many components of food, and it is designated as generally recognized as a safe nutrient in human food and animal feeds. It plays a vital role in the structural integrity of cell membrane; methylation metabolism; cholinergic neurotransmission; transmembrane signaling; and lipid and cholesterol transport.

The majority of the dietary choline consumed in the United States is in the form of phosphatidylcholine. Choline is absorbed from the lumen of the small intestine, and much of its metabolism occurs in the liver, where it is found primarily as phosphatidylcholine. In addition to this dietary supply, choline is found by de novo biosynthesis via an endogenous pathway in the liver by the sequential methylation of phosphatidylethanolamine using S-adenosylmethionine as the metyhl donor.

Next, we will discuss the safety profile of choline chloride that is the second criteria in this 503A evaluation. I will start with the available nonclinical data.

In the publicly available data, we located a risk assessment for choline chloride conducted by the EPA. The acute toxicity studies showed a large margin of safety for choline chloride in various species using various routes of administration. In an 8-month, repeat-dose toxicity study, and intraperitoneal injection of choline chloride in rats resulted in lung and liver abnormalities, as shown on this slide, at 3 months and at 6 months. These nonclinical toxicities were at much higher doses than proposed for clinical use.

The standard panel of genotoxicity assays did not show genetic toxicity activity, and choline chloride did not have genotoxic adverse effects. Choline chloride is important for the normal fetal and early postnatal development.

Male rats exposed to high doses of choline chloride showed a transient increase in adverse effects on spermatogonia in the first few days of the study -- [inaudible – audio gap] doses. These nonclinical toxicities observed were at much higher doses than proposed for clinical use. No long-term

carcinogenicity studies were conducted.

In the FAERS database, 6 cases were identified with use of choline chloride as a weight-loss injection that reported both exposure to choline chloride and at least one adverse event. These cases were confounded by the multiple medications in the injection or the multiple ingredient products that included choline chloride as one of the ingredients.

Six cases were reported in the CAERS database that included cases when choline chloride was one of multiple ingredients in energy drinks, muscle performance products, and nutritional supplements. Insufficient information was provided to interpret the contribution of choline chloride. Considering that there were many other substances in the dietary supplement, it was not possible to determine whether a causal connection existed between choline chloride and the adverse events reported.

The established adequate daily intake of choline is 550 milligrams for men and 425 milligrams for women, with an upper daily limit ranging up to 3 and a half grams per day. Adverse events have been

reported in clinical studies at doses much higher than the daily intake for food. Choline chloride has been associated with nausea, fishy body odor, sweating, diarrhea, and salivation. Hypotension is observed with daily use of more than 10 grams of choline chloride.

In most clinical studies, choline is found to be well tolerated and not associated with significant adverse events. The subsequent slides will discuss the third criteria in the 503A evaluation, and to do that, each of the uses proposed for the nomination will be discussed.

Choline chloride was evaluated for the treatment of liver diseases that included the nominator's proposed use for hepatic steatosis. Hepatic steatosis, or hepatic fat accumulation, or also called fatty liver, is not specific to a disease condition. It is a histological finding with the presence of large and small vesicles of fat, predominantly triglycerides, accumulating within the hepatocytes. For instance, if one were to consume one or two cocktails or glasses of wine tonight, the next day, it is quite conceivable that there will be the presence of hepatic steatosis.

The causes of the hepatic steatosis are shown on this slide. Typically, hepatic steatosis is not seen on imaging modalities. It is usually a benign finding, although we will discuss in the subsequent slides, in rare instances, over many years to several decades, chronic liver disease may develop as a result of the increased triglyceride accumulation, leading to chronic inflammation, hepatocyte degeneration, and scarring, with progression to fibrosis and potentially cirrhosis.

Next, we will discuss the nominator's proposed use for non-alcoholic fatty liver disease, abbreviated as NAFLD. NAFLD includes a spectrum of histological changes that includes simple fatty infiltration of the liver, also known as simple or isolated steatosis, or non-alcoholic fatty liver, abbreviated as NAFL, and also non-alcoholic steatohepatitis, abbreviated as NASH, N-A-S-H, which is an extreme form of NAFLD and is regarded as a leading cause of cirrhosis in the United States. Therefore, the histological changes of hepatic steatosis are seen across the NAFLD spectrum.

The figure illustrates a spectrum of NAFLD in that hepatic steatosis is not specific to a disease

condition. The histological changes are seen across the spectrum of NAFLD disease conditions. Typically, hepatic steatosis is transient and reversible. Most humans who have evidence of hepatic steatosis are asymptomatic and are not adversely affected by its presence.

The figure illustrates the histological subtypes and the associated risks for progression of NAFLD to other chronic liver diseases. As shown with the blue arrow, very few patients with simple, non-alcoholic fatty liver have progression to diseases like cirrhosis that is very serious or life-threatening.

At present, clinicians cannot predict which patients are likely to progress from benign steatosis, shown in box A on the upper-left side of the figure, to steatosis shown in box C on the upper-right side of this figure, or cirrhosis, shown in box E on the bottom of the figure.

If we assume that 100 million Americans have benign steatosis, or non-alcoholic fatty liver, and less than 4 percent wind up having cirrhosis, it is not end-stage liver disease. Non-alcoholic fatty liver is

likely to be 5 times less frequent an occurrence than in patients who have non-alcoholic steatohepatitis, or abbreviated NASH.

Benign steatosis, or NAFL, is reversible; for example, by abstaining from alcoholic beverages, weight loss and exercise, improved diet, management of hypertension and dyslipidemia, and glucose control in some diabetic patients. In conclusion, hepatic steatosis is not specific to a disease condition.

I will briefly discuss the relation of choline deficiency to development of hepatic steatosis and the non-alcoholic fatty liver disease spectrum. Theoretically, individuals who were to consume a diet deficient in choline can develop hepatic steatosis, and go on to develop liver damage in the form of NAFLD. It is because of the lack of dietary sources of phosphatidylcholine that limits the export of excess triglycerides from the liver in lipoproteins.

We discussed earlier in slide 11 about hepatic steatosis. This fat accumulation within the hepatocytes, predominantly in the form of triglyceride, can result in the non-alcoholic fatty liver disease

spectrum, and that includes histological evidence of hepatic steatosis. However, since the United States diet is rich in choline-containing foods, patients are unlikely to need a change in their diet in order to include choline-rich foods, or other nutritional supplements will be available to provide that choline source. It is also known that patients on long-term total parenteral nutrition that lack adequate choline in the form of phosphatidylcholine and phosphatidyl-ethanolamine can develop steatosis. This will be discussed further.

The next few slides, we'll discuss the evaluation of the information for effectiveness in NAFLD related to choline, including the current practice guideline recommendations.

Six practice guidelines pertaining to the treatment of NAFLD were identified. Use of choline chloride as a treatment of NAFLD was not mentioned in any of these treatment guidelines, stating that nutritional supplements do not show scientific data strong enough to support their recommendation as a treatment of NAFLD.

We evaluated three studies in patients with NAFLD. In one trial, 43 children and adolescents aged 4 to 16 years, with baseline liver biopsy confirming non-alcoholic steatohepatitis, were evaluated after 6 months oral treatment with daily supplement ProDHA Steatolip Plus pills, containing a combination of DHA, choline, and vitamin E. All subjects were to undergo liver ultrasound and blood test at 12 months.

The primary outcome measure of improvement in liver hypoechogenicity by liver ultrasound at 12 months decreased from 50 percent to 5 percent of patients in the subgroup analysis of the active-treated subjects with severe steatosis at baseline. However, the multiple ingredients in the treatment prevent attributing any benefit to choline.

Observational data from a cross-section analysis of 664 subjects with biopsy-proven NAFLD, who were enrolled in the multicenter, prospective, Non-alcoholic Steatohepatitis Clinical Research Network -- NASH CRN, abbreviated -- was conducted to determine whether there was an association between choline intake and the histologic severity of NAFLD or

NASH determined by liver biopsy. Baseline dietary data were based on recall and not prospectively collected.

The study showed that postmenopausal women with a reported choline intake less than one-half defined adequate intake had increased fibrosis. There was no intervention to determine whether liver disease improved with choline treatment.

Another study reported in 1946 evaluated choline for the treatment of cirrhosis of the liver with varying etiology. Due to the small number of responding patients, the multiple treatments provided, and the confusion regarding whether choline chloride was administered, it was not possible to draw any conclusions regarding the efficacy of choline chloride for the treatment of cirrhosis of the liver.

FDA has in its discretion opted to evaluate the clinical effectiveness of choline chloride for the unnominated use of supplementation in long-term total parenteral nutrition. Choline deficiency frequently occurred in long-term total parenteral nutrition patients, and this nutritional deficiency can lead to hepatic steatosis.

In 2012, the American Society for Parenteral and Enteral Nutrition published a position paper recommending that choline be routinely added to adult and pediatric parenteral nutrition formulations with even dosing guidance. However, we were not able to find data regarding the extent of use of choline chloride in parenteral nutrition if it is, in fact, added to parenteral nutrition. Although the ASPEN has made this recommendation, it is not clear that it has been implemented in the treatment of patients on total parenteral nutrition.

Sources of choline chloride for parenteral nutrition are available as egg phospholipid, which is primarily phosphatidylcholine or phosphatidyl-ethanolamine. An example of an FDA-approved product is Intralipid. The body can convert each to choline through metabolic pathways.

In conclusion, we could not find clinical evidence that choline administration will be effective in the treatment of NAFLD that is not related to a deficiency of choline.

Next, we will discuss the evaluation of the

information for effectiveness in atherosclerosis related to choline chloride. There were no scientific articles evaluating the use of choline chloride for the treatment of atherosclerosis and available in English that were cited by the nominator during the submission.

The nominator included two references for this use that FDA did not review because the articles were in a foreign language, although FDA identified three studies evaluating the use of choline chloride in atherosclerosis. One study included a 21-day treatment with a combination of 6 nutrients administered orally, including choline, in 12 patients following acute MI. Any benefit of choline could not be determined from the multiple ingredients used.

An 8-year cohort study in 16,000 women failed to show any difference in cardiovascular risk between women in the upper versus the lowest quartile of dietary choline intake. The prospective study of Atherosclerosis Risk in Communities cohort of over 14,000 men and women found that choline intake from food was not significantly associated with increased incidence of coronary artery disease, and a higher

choline intake was not protective for coronary heart disease. There is insufficient information to support the use of choline chloride for the treatment or the prevention of atherosclerosis.

Next, we will discuss the evaluation of the information for effectiveness in fetal alcohol spectrum disorder related to choline chloride. Optimal maternal nutrition is required to produce healthy offspring. When maternal nutrition status is compromised with alcohol use, essential nutrients are displaced or not obtained.

Although animal models have shown that choline chloride supplement has reduced some of the detrimental effects of alcohol consumption on fetal animals, randomized-controlled clinical trials evaluating the use of choline chloride to mitigate adverse effects on infant growth and cognitive function from prenatal alcohol exposure have had mixed results.

Two placebo-controlled studies evaluated the developmental outcomes during the infant's first year with prenatal choline chloride exposure following choline chloride treatment in women who reported

moderate to heavy drinking during their pregnancy. We also identified two trials in which choline was evaluated in children for the treatment of fetal alcohol syndrome that is from postnatal exposure.

A prospective prevention cohort study evaluated developmental outcomes in two randomized groups of alcohol-exposed infants born to pregnant women who reported moderate to heavy drinking during their pregnancy compared to a control population of infants born to women who reported low to no drinking.

Among the participants in the choline-exposed treatment arm, there was no improvement in cognitive outcome compared with the control group, and there was no difference between the group treated with only multivitamin supplements; that is group 2. The changes observed might have been solely due to the multivitamins and minerals.

In an exploratory randomized, double-blind, placebo-controlled clinical trial, 69 heavy drinkers recruited in mid-pregnancy were randomly assigned to either 2 grams of choline or placebo. Although the authors concluded that infants born to choline-treated

mothers were more likely to meet criterion on the eyeblink conditioning than the placebo group, it is not clear what the changes in eyeblink conditioning mean when interpreting neurodevelopmental outcome in these infants. At 12 months, the infants in the choline treatment arm had higher preferential looking at the novel stimulus on the Fagan test of Infant Intelligence, indicating better visual memory.

There were two trials in which choline was used and was evaluated in children for the treatment of fetal alcohol syndrome. This is from postnatal exposure to choline chloride. In a 6-week controlled trial in children with fetal alcohol spectrum disorders, choline or placebo was administered daily to 60 children, each aged 5 to 10 years of age.

Participants in the choline group did not improve in cognitive performance in any domain compared with placebo. In a 9-month controlled trial in children with fetal alcohol spectrum disorders, choline or placebo was administered daily to 60 children aged 2 and a half to 5 years of age. The study failed on the primary endpoint of global cognitive ability.

We were not able to find clinical effectiveness data that supported the proposed use of choline chloride with respect to liver diseases, including non-alcoholic fatty liver disease, hepatic steatosis, atherosclerosis, and fetal alcohol syndrome. There is insufficient information on the effectiveness of choline chloride for supplementation in long-term parenteral nutrition.

Lastly, we apply the fourth criterion; that is the historical use of choline chloride in compounded drug products. Choline chloride has been used in pharmacy compounding since at least 1954. Based on advertised information, though, choline chloride is most often used in compounded injectable products for weight loss in the United States. Choline chloride is available in the United Kingdom as part of a multiple ingredient product, indicated for the prevention of vitamin deficiency in certain conditions.

We have balanced the four criteria that was discussed to evaluate choline chloride for the 503A Bulks List. After considering the information currently available, a balancing of the four criteria weighs against choline chloride being added to the 503A Bulks

List. Thank you, and that's the end of my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you, Dr. Kasim.

We will now take clarifying questions for FDA presenters. Please use the raised-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 question with, "That is all for my question," so we can move on to the next panel member.

With that, do we have any questions?

Dr. Vaida?

DR. VAIDA: Yes. Thank you. Allen Vaida. I just have the questions on the use in parenteral nutrition. It seems that you said that there was no evidence of the use in parenteral nutrition. I assume

that was just looking for studies.

Was ASPEN ever contacted? I saw that the University of Maryland did that survey, but it didn't even look like ASPEN was even contacted in that survey? Could you answer that?

DR. KASIM: Yes. Thank you for the question. The information that I discussed regarding the ASPEN discussion from the slide was not after reaching out to ASPEN, but it was based on what was reported in the literature. I'll defer to my colleagues in OCQC to add additional context regarding the University of Maryland study report.

DR. HANKLA: Hi. This is Elizabeth Hankla. I can add a couple of comments about the M CERSI Maryland report. They did find evidence of compounding through a literature search, but they didn't identify anything for use in parenteral nutrition, and they did conduct a survey, which, again, they didn't find evidence of use in parenteral nutrition. I hope that helps.

DR. VAIDA: Okay. But you listed the groups of associations, and ASPEN wasn't one of them, or any board certified pharmacists in parenteral nutrition. I didn't

see them listed.

Could you just verify that they weren't?

DR. HANKLA: This is Beth again, Elizabeth Hankla. I do not see ASPEN listed as associations that were contacted.

DR. VAIDA: Alright. Thank you. No further questions.

DR. GULUR: Thank you, Dr. Vaida.

Dr. McElhiney?

DR. McELHINEY: I thought that I saw -- because I wasn't sure. I hadn't heard too much about choline chloride. I thought that I saw that it was being evaluated to become a commercial product and/or I thought I saw that it was already an orphan drug and being produced by another company.

Is that true?

DR. KASIM: This is Suhail Kasim. I'm not aware of an approved product distributed, as marketed, as choline chloride. I will again defer to my colleagues in OCQC, if anyone else has any information on the orphan product designation. An orphan product designation does not mean that the product is marketed.

It may mean that it has a certain designation provided by the FDA for product development. I'll let others elaborate on this.

DR. McELHINEY: Okay. Thank you. That's all I had.

DR. GULUR: Thank you.

Dr. Gura?

DR. GURA: Yes. Hi. Actually, I can comment on the studied IV choline chloride injection. Back in 2018, it actually did receive orphan drug designation, and it's currently in phase 2 trials. It might even be finished now.

I am a member of ASPEN and board certified in nutrition, so I'm familiar with this work. There have been several centers that have been using choline in their parenteral nutrition as a means to prevent some of the hepatic complications we see with long-term PN use. But I'm looking forward to seeing the results of the phase 2 trial because it's a farmer-made product as opposed to a compounded product.

I just wanted also to find out how do the decisions we make today impact this phase 2 trial study

drug? Are they two separate issues?

DR. KASIM: I will respond to that. This is Suhail Kasim. I will respond to that initially, and if my colleagues have additional context to add to that information. Products that are being developed for marketing purposes will not be affected, based on the decisions made here. That is independent.

Does that answer your question?

DR. BORMEL: And this is Gail --

DR. KASIM: Sorry, Gail.

DR. GURA: Yes, it is. Thank you very much.

DR. BORMEL: And this is Gail Bormel. I was just going to echo what was just said. Yes. They're two separate processes. They're distinct.

DR. GULUR: Have your questions been answered?

DR. GURA: Yes. Thank you.

DR. GULUR: Wonderful.

Dr. Bui?

DR. BUI: Hi. Yes. Dr. Bui here.

Dr. Kasim, you mentioned in one of your slides that choline has been used in pharmacy compounding since at least 1954. That's a long time. Do you have any

information -- I mean not since 1945 -- any other information that relate to weight loss in the U.S. or how it's been used in the UK, I believe, for vitamin deficiencies in certain conditions?

Is there any new information available regarding pharmacy compounding and maybe specific to any safety concerns in that environment?

DR. KASIM: This is Suhail again. My colleagues in OCQC can further elaborate on the history of use in compounding and various uses.

The slide that was projected did specifically mention that it was in association with weight loss products. The FAERS and CAERS cases that I discussed in the slides earlier did report adverse events that you can consider serious. However, it is not possible, because in those weight-loss products, either in weight-loss products or when it was used for the purposes of treating a patient, it may have been used with additional substances or additional products.

So to discern whether choline chloride was a causative agent for adverse events, it was difficult to interpret, but what we do know is from clinical studies,

there was a clinical pharmacology study that was included in the evaluation, and that included an IV injection of choline chloride up to 8 milligrams. I saw that there was data for up to 8 milligrams, and that was in patients with hepatic steatosis or in non-alcoholic fatty liver. But in some patients, there needed to be downward dose titration. That means there were adverse events noted, those which were discussed earlier.

That gives you the context of clinical safety when it was used as a weight-loss product. Regarding the products used outside the United States, well, just as you have questions, I had questions when I was looking into this issue. I had to web search to see are we using weight loss and how is it being used as an IV product if it is a dietary supplement.

So to answer that question, I saw that there were FDA recalls on some of those products, and some of these products are available outside the United States, in Europe, which are marketed. So I cannot provide any more information regarding those products outside the United States that are available. I'll let my colleagues in OCQC add additional context to these

therapies using compounding.

DR. BORMEL: Thank you. This is Gail Bormel. I just want to emphasize that we don't routinely get adverse event reporting for compounded drugs made under Section 503A of the FD&C Act because it's not required. If there are adverse events, there are many adverse events associated with a particular compounded drug product that's being made under Section 503A, there's no mechanism to require reporting of those adverse events to FDA. What we get is just a snippet of what is voluntarily reported to us, so you have to look at the adverse events under that context.

DR. BUI: Thank you, Dr. Kasim and Gail.

I have a second question. We discussed here about how choline is being used for NAFLD and NASH. Did the agency look at any investigational drugs out there being developed by other companies at this point for both NAFLD and NASH, and that may be an option for patients if choline's not available?

DR. KASIM: Before I go into discussion -- this is Suhail Kasim again. My colleagues for the Division of Hepatology are available to answer questions. But

before I approach them, I'm not sure it is a venue to discuss products under investigation, new drugs, or that are being considered in development for marketing applications in this venue. I believe there may be. I'll leave it at that.

So if my colleagues in the Division of Hepatology or other colleagues in OND want to provide additional context to respond to Dr. Bui's question? Thank you.

DR. ANANIA: Frank Anania from the Division of Division of Hepatology and Nutrition.

Hello?

DR. LAI: Hello. This is Dr. Lai, hepatology at UC San Francisco. May I speak?

DR. GULUR: Yes, Dr. Lai. Go ahead and speak.

DR. LAI: Great.

I am one of the hepatology colleagues, and I am not aware of the use of choline chloride for the specific treatment of hepatic steatosis or non-alcoholic fatty liver disease.

DR. GULUR: Thank you.

DR. LAI: I do have a separate question aside

from that when it's my turn.

DR. GULUR: Please go ahead, Dr. Lai.

DR. LAI: Thank you.

What we do see in hepatology is that hepatic steatosis in the setting of a long-term parenteral nutrition is common, so we do see fat in the liver as a result of parenteral nutrition. The studies that were shown by the speaker is that one of the mechanisms of this could be choline deficiency.

I do recognize that you said that we are unaware of the frequency by which choline is added to parenteral nutrition formulations, but how would choline be added to parenteral nutrition if it is not approved today? And I wonder, if it's not approved on the bulk drugs list, is that a barrier to adding it to parenteral nutrition, and could we be actually causing harm to patients who require long-term parenteral nutrition, particularly given the relatively mild toxicities associated with choline infusion?

DR. KASIM: Dr. Lai, probably Dr. Anania intends to respond, but --

DR. ANANIA: Yes.

DR. KASIM: Okay. Go ahead, Dr. Frank.

DR. ANANIA: Yes. First of all, I wanted to concur with the statement that there is no evidence for clinical effectiveness to treat NASH or NAFLD. That was a question that came up, and I had trouble getting through because I was double-muted.

Regarding the addition of choline chloride to parenteral nutrition, I'm a hepatologist as well, in the Division of Hepatology and Nutrition. This is a complex question, but to be brief, all FDA-approved lipid supplements for parenteral nutrition include an adequate amount of phosphatidylcholine and phosphatidyl-ethanolamine, which, as the speaker indicated, can be readily converted to choline.

There are other issues, as I'm sure the hepatologists on the committee knows, that play a role in the development of parenterally associated fatty liver disease. I think that is all I'd like to say about that. Thank you.

DR. LAI: Thank you. That's it for my question.

DR. GULUR: Thank you.

Dr. Bui and Dr. Gura, I do see your hands are still up. Is it because you still have questions?

DR. BUI: This is Dr. Bui. Thank you for the answer. I have no further comment.

DR. GULUR: Thank you, Dr. Bui

Are there any other questions, any further questions for our presenters?

(No response.)

DR. GULUR: Seeing none, we will now proceed with the nominator presentation. We have one presentation from Dr. Paul S. Anderson, who is speaking on behalf of the American Association of Naturopathic Physicians

Dr. Anderson?

DR. ANDERSON: Okay. I'm assuming you can hear me.

DR. GULUR: Yes, we can.

DR. ANDERSON: Alright. Thank you.

Nominator Presentation – Paul Anderson

DR. ANDERSON: Well, thank you for this time, and thank you, FDA, for those very excellent presentations. I'm just going to focus on a couple of

properties.

One of the things to point out is we have a lot of data on dietary requirements around all nutrient systems, specifically choline in this case, and we have reasonable data on the effects of deficiency in a number of areas.

Now, in one of the reviews, as listed here, we have preterm birth listed there, but about 1 percent of all births have been fetal alcohol syndrome, which there are not many approved treatments. Also as pointed out, there are really no FDA-approved choline drugs with the exception of the lipid product, which has been mentioned already. So the addition and the need for choline products for physicians through compounding is necessary.

Overall, in preterm infants, choline deficiency has been noted, and it's also been noted that breastfeeding does not supply enough choline to correct said deficiencies. This would also apply to other infants, including those affected by fetal alcohol syndrome. We have some other, just general, information here as related to deficiency, especially in preterm

infants.

In my presentation, I've used endnotes, and because of the way that this screen is, I don't have access to the endnotes, but we have the references cited there. Generally speaking, in babies with fetal alcohol syndrome, their choline supplementation was well tolerated and very low amounts of adverse events. I believe in the prior presentation, cognitive characteristic changes were shown. What I would say is, in particular, in reference number 8, there were positive cognitive changes noted in the fetal alcohol syndrome of babies.

To reiterate, the supplementation of choline is beneficial for children during developmental stages, especially with respect to neurological development. Because right now the only FDA-approved treatment is parenteral treatment, there isn't anything in the 503 setting that would be available to be used for an infant for supplementation.

The other data that is out shows that both in animals and humans, there are improved pregnancy outcomes with choline supplementation prenatally, and as

this particular citation notes, most pregnant women in the U.S. are not achieving choline intake recommendations of 450 milligrams a day. So while it is certainly available through the diet, it's not being generally achieved in pregnancy. Also, although this is not one of the nominated areas, there is, as most know, an increase in neural tube defects in women achieving less than 300 milligrams of choline, which does fall into the previous slide as well.

I think this was well covered by the FDA presentation, officially recognized since 1998, although it's been traditionally used in compounding since the 1950s at the very least. In a different citation, number 13 at the end, it's noted that choline intakes in people other than in pregnant women, but including pregnant women, are below adequate intake levels, established by IOM.

Now, ASPEN's been brought up a few times, and this is essentially, I think, the same information that was given in the FDA presentation. ASPEN is calling for a parenteral choline product to be developed and available.

I do not have a slide on it, but I wanted to mention as a follow-up to some previous discussion that we just had, that there is a choline chloride intravenous product that one year ago, 5-26-2020, was granted a fast track by FDA for the indication of intestinal failure associated liver disease, IFLD; and that is a choline chloride IV product specifically developed by Protara Therapeutics. It is, I believe, now in phase 3 trials.

While the parenteral choline product is hopefully going to be available, in the meantime, a choline chloride parenteral product is not available outside of its donor products in the lipid emulsions, et cetera. In this particular presentation, I wanted to focus on fetal alcohol syndrome children, the potential for use in prenatal, and then the availability through 503A compounding for a choline chloride intravenous product because even though there's a fast track for a manufactured product, it is not currently available, to the degree that I can find, in any FDA information anyway.

One reason for compounding that is important is

there are times when people are incompatible, at least due to allergy or sensitivity, with the currently approved products. As has been mentioned a couple of times in previous discussion and the FDA presentation, we have a parenteral source as a phospholipid-approved product, and that one was mentioned a few times.

In the case of compounding, if you want a choline donor that is not from an egg phospholipid source -- say somebody has egg allergy, which there are data that that does exist in humans -- choline chloride is the preferred option for a non-egg-based choline product. So in the case of a 503 application, choline chloride would leave an inclusion that did not cross over with any sensitivities for the egg base.

Those are the references, so I will yield now for the Q&A

Clarifying Questions from the Committee

DR. GULUR: Thank you.

We will now take clarifying questions for the nominator presenter. Please use the raised-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 question with, "That is all for my question," so we can move on to the next panel member.

With that, do we have any questions for our nominator presenter?

Dr. Ganley, I see that your hand is raised. Did you have a question for our nominator presenter?

DR. GANLEY: Yes, for Dr. Anderson.

I guess I'm trying to understand here from your presentation, you seem to have different buckets of things. One is nutritional supplementation, which presumably could be done orally and for which there are dietary supplements available. But then you're getting into the treatment of diseases for which we have not had any evidence of effectiveness that we were able to find for the nominated conditions.

So I guess I'm wondering where the line is drawn between something that would just go on the 503A list to treat conditions for which we don't know that they would actually work versus conducting studies under an investigational new drug application to determine effectiveness.

DR. ANDERSON: Yes. I think you make a reasonable point. There certainly is -- and I think that could be said for a lot of the 503A products. There's a lot of crossover with, say, nutritional supplement availability.

One of the things in regard to the bucket, as you mentioned, of nutritional use or nutritional supplement use, say, for preventing deficiency, as an example with 503A, there are in many cases the need for 503A to compound a nutritional product that may include something such as, say, choline chloride, and also potentially other components of the nutritional augmentation.

If choline chloride was a bulk substance for 503A and the physician needed that part of the compound, then the compound that was being ordered would be

obviously deficient in that area. And like in the discussion of, say, methylcobalamin, there is oral availability through the supplement world, it would divorce the ability of the 503A pharmacy to be able to use that in the compound as it were.

With respect to the disease states, the disease state that I focused on was fetal alcohol. I cannot retrieve anything on my screen and leave the FDA portal up, so I don't have access to those notes. As many things are not extremely conclusive with respect to fetal alcohol, but there is positive data that I see there. So that's why I focused on that particular disease.

DR. GANLEY: Yes. Just to follow up on that, I'm not sure I saw the data for the effectiveness in treating fetal alcohol syndrome, and I think the issue comes down to using a treatment, particularly in very young children, for which we don't have evidence that it actually provides benefit.

So I'm trying to understand, well, why would we do that under 503A versus actually getting it done under an IND, where there's informed consent, and

understanding whether it does have some benefit in that population of patients.

DR. ANDERSON: No. That's a very good point, especially with respect to fetal alcohol in children, and it certainly would be exactly the same as the methyl B12 in the autism discussion. That certainly would be the preferred and the safest pathway.

If used appropriately in adults and children, choline is overwhelmingly safe with very low adverse events, so much like in the B12 discussion, you could still have it available in 503A for adults and children, and still pursue it through the IND process.

DR. GULUR: Did that answer your question?

DR. GANLEY: Yes.

DR. GULUR: Thank you.

Do we have anyone else who has a question?

(No response.)

DR. GULUR: Seeing as there are none, thank you very much for your nominator presentation. We appreciate it.

We will now begin the open public hearing session. I would like to state into the record that

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

We have an opportunity now for clarifying questions. We will now take remaining clarifying questions for all the choline chloride presenters. Please use the raised-hand icon to indicate that you have a question and remember to put your hand down after you have asked your question. Please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

If you wish for a specific slide to be displayed, please let us know the slide number, if possible. As a gentle reminder, it 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 question," so we can move on to the next panel member.

With that, do we have any questions for clarification?

(No response.)

DR. GULUR: Seeing as there are no clarifying questions for our presenters, the panel discussion will now start. We encourage all our panel members to use this opportunity to bring up comments or summarize any concerns.

Dr. Vaida?

DR. VAIDA: Yes. I just had a question, probably, from two of the panel members. I think was Dr. Gura that mentioned that choline chloride is available for parenteral nutrition right now in a study.

Does that mean that anyone could get that right now?

DR. BORMEL: No, that's an investigational product. Oops, I'm sorry.

DR. VAIDA: Okay. Thank you.

DR. GULUR: Does that answer your question, Dr. Vaida?

DR. VAIDA: Yes, it does. Thank you.

DR. GULUR: No further questions I'm assuming.

Dr. Bogner?

DR. BOGNER: Thank you. I find the choline literature very difficult because people refer to lots

of different cholines as choline, whereas free choline is also choline, in addition to the choline chloride, of course, which is also free choline.

I'm trying to determine -- and I'm wondering if any of the panel members can clarify, or even perhaps Dr. Gura, who's obviously an expert in this field -- what is the advantage of choline chloride versus choline in some sort of phosphatidylcholine? Is there an advantage or a disadvantage?

That's it. Thank you.

DR. GURA: It's ok for me to answer?

DR. GULUR: Yes, please.

DR. GURA: I'm not an expert in choline. I'm familiar with some of the literature that has been used for the past, I think, over 20 years now in attempts to mitigate the hepatotoxicity of parenteral nutrition. I think the thought is that the adequate amounts of choline available in the phosphatidylcholine in the emulsifier used in IV lipid emulsions, not all patients receive lipid emulsions in adequate amounts. Some only get enough to prevent essential fatty acid disease. That might be one of the considerations.

I know in our practice, we don't really consider the amount of choline present in the lipid emulsions, and as I mentioned previously, I'm more intrigued with learning about the results from the recent trials with the parenteral choline chloride that's underway, I guess now in phase 3.

DR. BOGNER: Thank you, Dr. Gura.

I'm wondering if anyone else has anything to add, and if not, thank you all.

DR. PATEL: Hello? I had my hand raised. This is Kuldip.

DR. GULUR: Yes, Dr. Patel. I think that was just Dr. Bogner saying that she was done with her questions.

Dr. Patel, please ask yours.

DR. PATEL: Yes. Thank you.

To Dr. Gura's point, it seemed like, based on Dr. Anderson's presentation, the subset of populations of infants or children who may potentially have an egg allergy, who are on long-term TPN, would likely be running into a situation of not having a therapeutic option available if the committee decides to not add it

to the bulk list.

So I'm wondering if there's any data on that subset population that might either had suffered adverse events or maybe negative health outcomes as a result of not having that option available. I'm just wondering if there are any case reports or any data that might be out there with regards to those patients suffering from such an issue.

(Pause.)

DR. PATEL: End of my question.

DR. GURA: I'm not aware of any, except for what was in the adult literature, not in the pediatric literature, at least in regard to parenterally fed children.

DR. GULUR: Thank you.

Dr. Patel, does that answer your question?

DR. PATEL: It does. Thank you.

DR. GULUR: Is there anyone else who has any comments or questions for this phase?

(No response.)

DR. GULUR: Seeing none, the committee will now turn its attention to address the task at hand, the

careful consideration of the data before the committee, as well as the public comments.

Committee Discussion and Vote

DR. GULUR: We will proceed with the question to the committee and panel discussions for choline chloride. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate, except at the specific request of the panel.

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

DR. STEVENSON: Question 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 the voting will begin.

If you are a voting member, you will be moved to a breakout room and the 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 a 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. GULUR: Dr. Patel, do you still have a question?

DR. PATEL: No, I do not. I'm sorry. I'll take the hand down.

DR. GULUR: No worries. Thank you.

Seeing as there are no clarifying questions on the voting process, I will now read the question at hand into the record.

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

Do panel members have any questions or issues with the wording?

(No response.)

DR. GULUR: To clarify, 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 the voting on question for choline chloride.

(No response.)

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 votes 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, 11 noes, and zero abstentions -- 1 abstention. My mistake; 1 abstention.

DR. GULUR: Thank you, Takyiah.

To confirm, 2 yeses, 11 noes, and 1 abstain; correct?

DR. STEVENSON: Correct, yes. Thank you.

DR. GULUR: We will now go down the list and

have everyone who voted state their name and vote into the record. You may also provide justification for your vote, if you wish to.

We will start with Dr. McElhiney.

DR. McELHINEY: Linda McElhiney. I vote no.

DR. GULUR: Dr. Fensky?

DR. FENSKY: Tim Fensky. I voted no.

DR. GULUR: Padma Gulur. I voted no.

Dr. Gura?

DR. GURA: Kathleen Gura. I vote no.

DR. GULUR: Dr. Rebello?

DR. REBELLO: Elizabeth Rebello. I voted no.

DR. GULUR: Ms. Fusco-Walker?

MS. FUSCO-WALKER: Sandra Fusco-Walker. I abstained due to technical difficulties. I could not hear the presentation.

DR. GULUR: I'm sorry to hear that, Ms. Fusco-Walker.

Dr. Lai?

DR. LAI: Jennifer Lai. I vote no.

DR. GULUR: Dr. Liangpunsakul?

DR. LIANGPUNSAKUL: Suthat Liangpunsakul. I

vote no.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Robin Bogner. I voted yes. I didn't feel like there was very good information either way and don't agree with some of what was said previously, that people wish that we could revisit things in the future again. I find they don't get revisited very quickly, so I went on the side of access.

DR. GULUR: Thank you, Dr. Bogner.

Dr. Gupta?

DR. GUPTA: Hi. Thank you. I voted yes. Similarly, I believe in the situation for patient access based on the discussion about alcohol syndrome, and also the pervasiveness of this condition, and also the need for access in this condition, I felt a compelling reason to vote yes; so thank you.

DR. GULUR: Thank you, Dr. Gupta.

Dr. Sun?

DR. SUN: This is Jeanne Sun. I voted no.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Allen Vaida. I voted no.

DR. GULUR: Dr. Patel?

DR. PATEL: Kuldip Patel. I voted no.

DR. GULUR: Dr. Desai?

DR. DESAI: Seemal Desai. I voted no.

DR. GULUR: Thank you.

Takyiah, can we confirm that we've recorded. everyone's vote?

DR. STEVENSON: Yes, I confirm we've recorded everyone's vote.

Thank you so much, Dr. Gulur.

DR. GULUR: Thank you.

With this, we end the choline chloride discussion. Thank you, everyone.

We will now take a break until 4:30. We will reconvene, as I just stated, at 4:30 Eastern time for the oxitriptan topic. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. Thank you.

(Whereupon, at 4:20 p.m., a recess was taken.)

DR. GULUR: Welcome back, everyone. We will now proceed with the FDA presentation on oxitriptan from Dr. Madeline Wolfert.

FDA Presentation – Madeline Wolfert

DR. WOLFERT: Thank you so much.

Good afternoon. My name is Madeline Wolfert. I'm a physician with the Pharmacy Compounding Review Team in the Office of New Drugs, and I will be discussing oxitriptan, also known as 5-hydroxytryptophan or 5-HTP.

I would like to recognize the entire evaluation team, including Drs. Lopez and Hankla, as well as acknowledge the contribution of many other FDA colleagues who helped in this effort, and our special thanks to the Division of Rare Diseases and Medical Genetics in the Office of New Drugs.

As I'll discuss later in this presentation, we did not perform a full chemistry and nonclinical evaluation for this review, but I'd like to recognize and appreciate the presence of our colleagues from chemistry and nonclinical disciplines, who are present in this meeting to help address any relevant concerns should they come up.

Oxitriptan, again, also known as 5-hydroxytryptophan or 5-HTP, is being considered for

inclusion on the list of bulk drug substances for use in compounding under Section 503A of the FD&C Act, also known as the 503A Bulks List. Oxitriptan is proposed for oral use in the treatment of the rare disease tetrahydrobiopterin or BH4 deficiency.

The next few slides offer some background on the regulatory timeline of compounded oxitriptan. In June 2015, oxitriptan was discussed at the PCAC meeting. Oxitriptan was previously nominated for use in the treatment of depression and sleep disorders.

FDA evaluated oxitriptan for inclusion on the 503A Bulks List for the nominated conditions, depression and sleep disorders. Treatment for BH4 deficiency was not considered, as it was not nominated for this condition.

FDA did not recommend inclusion on the list due to a lack of adequate evidence of effectiveness, as well as safety concerns, including risk for serotonin syndrome and inadequately treated depression. Based on the information presented, the PCAC voted not to include oxitriptan on the list, with 10 noes and 2 yeses. Taking into consideration the PCAC's advice, FDA

determined not to include oxitriptan on the list.

In December 2016, FDA published a proposed rule to not include oxitriptan on the 503A Bulks List. FDA received comments on the proposed rule, but none identified treatment of BH4 deficiency as a proposed use of oxitriptan. In February 2019, the final rule was published in which oxitriptan was not included on the list.

Thereafter, several healthcare providers and caregivers of patients with BH4 deficiency contacted FDA, expressing that oxitriptan is an essential and standard treatment for BH4 deficiency. FDA received a citizen petition communicating that compounded drug products containing oxitriptan are used to treat patients with BH4 deficiency.

In July 2019, in light of the information brought to our attention, FDA issued guidance that it generally does not intend to take action against compounders who use oral oxitriptan to compound for identified individual patients with BH4 deficiency, and now we are re-evaluating whether oxitriptan should be added to the 503A Bulks List for BH4 deficiency.

This slide lists the criteria we consider when conducting evaluations for the 503A Bulks List. These include the physical and chemical characterization; clinical and nonclinical safety; available evidence of effectiveness or lack of effectiveness; and historical use in compounding.

The FDA's 2015 evaluation of oxitriptan reviewed physical and chemical characterization and nonclinical safety. Thus, full chemistry and nonclinical assessments were not performed again for our current evaluation. Today's presentation focuses on application of these criteria to oxitriptan in the treatment of BH4 deficiency.

As just mentioned, the physical and chemical characterization of oxitriptan was evaluated in 2015, and the following is the summary.

Oxitriptan is a relatively simple, well-characterized active pharmaceutical ingredient. It is likely to be stable in solid and solution formulations. It is unlikely to contain significant amounts of toxic impurities. From a chemistry perspective, oxitriptan appears to be acceptable for inclusion on the list.

Nonclinical safety data for oxitriptan was also evaluated in 2015. The available nonclinical data on oxitriptan did not identify any particular safety concerns. There is no publicly available information on carcinogenic potential and minimal available data on general toxicity and mutagenicity.

In the next few slides, I'll be presenting clinical safety information on oxitriptan. Consistent with FDA's 2015 evaluation, common adverse reactions of oxitriptan include gastrointestinal symptoms such as nausea, vomiting, diarrhea, as well as headache and dizziness.

There is also the potential risk of serotonin syndrome. Serotonin syndrome is a clinically diagnosed condition that occurs with hyperstimulation of serotonin receptors in the body. It presents with a variety of symptoms that may include restlessness; confusion; shivering; tachycardia; hypertension; diarrhea; muscle twitches; hyperthermia; seizures; loss of consciousness; or even death.

Based on the mechanism of action as a chemical precursor in the biosynthesis of serotonin, concomitant

use of oxitriptan with antidepressant drugs could result in serotonin syndrome.

In our safety evaluation, we also searched for reports listing oxitriptan as an ingredient in an adverse event report. CSFAN collects reports of adverse events involving food, cosmetics, and dietary supplements in the CSFAN Adverse Event Reporting System or CAERS.

A search of CAERS was conducted in July 2018, with an interim follow-up search in March 2021, for reports listing oxitriptan as an ingredient in adverse event reports. A total of 249 reports were identified. Most of the reports involved an oxitriptan product formulated with multiple other substances or concomitant use of other products.

There is also wide variability in the quality of the reports, and some provide sparse or confusing descriptions. This limits the determination of a causal relationship between oxitriptan and the adverse event reported. The database does have reports for oxitriptan identifying possible serotonin syndrome.

An example of reported serotonin syndrome in

the CAERS database described a 35-year-old female taking an unspecified dose of oxitriptan and PharmaGABA-250, a dietary supplement containing gamma aminobutyric acid 250 milligrams. She developed palpitations, elevated blood pressure, and bilateral cramping up her calf muscles. She was diagnosed with serotonin syndrome after a cardiac workup was negative, and she had an elevated serotonin level on lab testing. Two months later after stopping supplements, the serotonin level was within reference range, and she was asymptomatic and feeling back to normal.

No clinical trials assessing the safety of oxitriptan in patients with BH4 deficiency were identified. Specifically in patients with BH4 deficiency, the most common adverse effects reported for oxitriptan were gastrointestinal symptoms such as nausea, vomiting, diarrhea, and abdominal pain. Irritability, motor disorders, such as choreoathetoid, dyskinetic, or myoclonic movements, and sweating were also reported.

In most cases, oxitriptan is administered in combination with other medications and interventions to

treat BH4 deficiency such as L-dopa in combination with a decarboxylase inhibitor like carbidopa; BH4 supplementation with a synthetic analog such as sapropterin dihydrochloride; and/or a reduced phenylalanine diet. This could confound interpretation of adverse effects.

Due to these safety risks I've discussed, specifically serotonin syndrome associated with oxitriptan use, if FDA places oxitriptan on the 503A Bulks List, FDA intends to make safety information about the use of oxitriptan available to prescribers, pharmacists, and the public through information on FDA's website, in its safety guide, or through other appropriate mechanisms.

I will now switch gears to talk about some background on BH4 deficiency, the role of BH4 in the body, and briefly describe the disease and its treatment. BH4 deficiency is a general term for a group of inborn errors of metabolism characterized by deficiency of the cofactor BH4. I apologize for the busy slide, but it helps to illustrate the role of BH4 in these pathways. In this figure, BH4 is highlighted

in red.

BH4 is an essential cofactor for multiple enzymes, including phenylalanine hydroxylase, tyrosine hydroxylase, and tryptophan hydroxylase. A cofactor is a substance in the body that is necessary for the proper function of certain enzymes.

Tyrosine hydroxylase and tryptophan and hydroxylase are key enzymes involved in the conversion of precursors L-dopa and oxitriptan to critical neurotransmitters dopamine and serotonin, respectively. Oxitriptan is denoted as 5-OH-Trp in this figure and is highlighted in yellow. BH4 deficiency disease is caused by pathogenic mutations in the genes encoding the enzymes in its biosynthesis or regeneration pathways, resulting in depletion of available BH4.

Thus, BH4 deficiency really comprises a group of heterogeneous neurotransmitter disorders. Deficiency of BH4 limits its availability as a cofactor, and thereby BH4 deficiency typically manifests with hyperphenylalanemia and deficiency of the neurotransmitter precursors L-dopa and oxitriptan. Diagnosis is usually made based on elevated

phenylalanine levels detected on the neonatal phenylketonuria or PKU screen. Workup typically includes analysis of blood and urine, cerebrospinal fluid, and gene sequencing.

BH4 deficiency disorders are commonly characterized by motor dysfunction, impaired muscle tone, movement abnormalities, intellectual disability, and seizures. Symptoms of BH4 deficiency typically present in infancy, such as in the first few weeks of life with poor suck and decreased spontaneous movements, but are often noted around 4 months of age.

BH4 deficiency is a rare disease estimated to affect approximately 1 in 1 million individuals in the general population. The exact prevalence is difficult to determine given variability in newborn screening protocols, and that some cases, especially if mild, may go undiagnosed or misdiagnosed.

The treatment strategy described in the literature is two-pronged, first, limitation of hyperphenylalaninemia through a restricted phenylalanine diet and/or BH4 replacement; and secondly, in combination with phenylalanine control, substitution of

depleted neurotransmitters by using the precursors oral oxitriptan and L-dopa/carbidopa.

We were unable to find information on alternate routes of administration, so our evaluation is limited to oral administration of these medications. Treatment should be initiated as early as possible to optimize neurodevelopmental outcomes and improve and prevent worsening of symptoms. Late detection and late initiation of effective treatment can lead to irreversible brain damage.

Treatment is focused on managing the symptoms and preventing long-term nervous system damage. Patients with BH4 deficiency require close and lifelong follow-up. Pediatric patients require frequent visits due to dosing titration and dose adjustments with weight gain.

In the next slides, I'll present the information we found on the effectiveness of oxitriptan for BH4 deficiency and some case reports. Oxitriptan is considered first-line treatment in BH4 deficiency in the literature. A consensus guideline for the diagnosis and treatment of BH4 deficiencies published in 2020 included

a strong recommendation that from a biochemical standpoint, oxitriptan is considered first-line treatment, as benefits clearly outweigh adverse effects.

NORD, the National Organization for Rare Disorders, identifies oxitriptan as a standard therapy used to restore neurotransmitter balance. The recommended pediatric target dose for oxitriptan is variable in the literature, but it has been cited as 4 to 10 milligrams per kilogram per day orally. The starting dose is 1 to 2 mgs per kg per day, typically divided in 3 to 6 doses per day. This is slowly titrated up based on clinical response, side effects, and weight gain in pediatric patients. Measurement of neurotransmitter metabolites in cerebrospinal fluid may also be helpful in dose titration.

Numerous case reports worldwide regarding treatment for BH4 deficiency with oxitriptan have been published. Some case report examples in children include, an infant showed steady improvement in myoclonus, uncontrolled movements, hypersalivation, and head control when treated with oxitriptan and L-dopa; a 27-month-old child showed improvement in areas of

receptive language and motor strength, in addition to increased alertness and responsiveness after treatment with L-dopa, carbidopa, and oxitriptan.

A long-term, follow-up report of 5 patients with BH4 deficiency showed the range of disease severity and variation in treatment response. Some patients demonstrated improvement in symptoms, such as swallowing difficulties and seizures, with oxitriptan and L-dopa/carbidopa.

Here's what we found on the historical use of oxitriptan in compounding. Based on published literature, oxitriptan has been used in pharmacy compounding for BH4 deficiency since at least 2011, however, it can be presumed that it's been used since the 1970s, when dosing for children with BH4 deficiency was first described.

We have revisited whether oxitriptan should be added to the 503A Bulks List, addressing the physical and chemical characteristics, safety, effectiveness, and historical use in compounding of oxitriptan for the treatment of BH4 deficiency. Based on this information, the agency has considered a balancing of the criteria

weighs in favor of oxitriptan for oral administration being added to the 503A Bulks List. Thank you very much. This concludes my presentation.

Clarifying Questions from the Committee

DR. GULUR: Thank you for that presentation.

We will now take clarifying questions for FDA presenters. Please use the raised-hand icon to indicate that you have a question and remember to clear the icon after you have asked your question. When acknowledged, please remember to state your name for the record before you speak and direct your question to a specific presenter, if you can.

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

With that, do we have any questions?

Dr. Vaida?

DR. VAIDA: Yes. Thank you.

I just want to clarify, as of right now, oxitriptan isn't on the list, but the FDA has a guidance that says that it can be used for oral compounding for BH4 deficiency with restrictions.

Is that correct?

DR. WOLFERT: Yes, that's correct.

Pardon me. Can I answer? It's Madeline Wolfert.

DR. GULUR: Yes. Yes, please.

DR. WOLFERT: Yes. It was voted in 2015 not to be included on the list, and it was subsequently not included on the list. The guidance allowed for compounding with those certain restrictions, oral administration, and for patients with BH4 deficiency with the intention to re-evaluate it for inclusion on the 503A Bulks List.

DR. VAIDA: Okay. Just to follow up, then, if we do include it on the list, then, once again, it can be used for insomnia and depression with the adverse events that have been identified.

Is that correct?

DR. WOLFERT: So including it on the list would

not limit the indications, yes. And I can also refer this question to Gail Bormel in OCQC for additional information as well.

DR. BORMEL: Yes. This is Gail Bormel. What was said is correct.

Dr. Vaida, when we put out that guidance, it was included as policy to tell people we would not object to the compounding of drug products using oxitriptan because we had, actually, a final rule which said that oxitriptan would not be placed on the bulks list. So because we found out about this use for oxitriptan after the final rule published, we issued the guidance so that 503A compounders could still use it within the limits described in the guidance.

What we're now doing is we are revisiting whether oxitriptan for oral administration should be placed on the 503A Bulks List, and it is correct that when we place oxitriptan on the list, we cannot limit the indication or what the bulk drug substance that's made into a compounded drug product would be used for.

DR. VAIDA: Okay. I'm sorry.

One other follow-up, is there any in between,

that we could just stay with what's current, that is not on the list?

DR. BORMEL: To retain the final guidance?

DR. VAIDA: Correct.

DR. BORMEL: It's possible that we would not have to alter the way things are right now. But remember, under 503A, there is a scheme that is described in order to tell compounders under Section 503A what type of bulk drug substances that can be used in compounding: those bulk drug substances that can be used or those that are components of FDA-approved drugs; those that are subject to an applicable USP and NF monograph; or those that appear on the 503A Bulks List.

There's no mention in the law of a discretion policy and guidances that would implement the list. Because we had new information about oxitriptan, we brought it back to the expert, the 503A pharmacy compound -- I'm sorry, the Pharmacy Compounding Advisory Committee to reconsider.

DR. VAIDA: Okay. No further questions. Thank you.

DR. GULUR: Thank you, Dr. Vaida.

Dr. Bormel, if I could follow up on Dr. Vaida's question just for some elaboration and clarification, the FDA recommendation, the presentation seems to be for a specific indication, but the side effects for other indications, which were a concern to start, still exist.

Is the recommendation to include this in spite of those potential side effects?

DR. BORMEL: I think definitely we're looking at these bulk drug substances because we found out about the use of oxitriptan in compounded drugs for BH4 deficiency. As is the case, when we do add bulk drug substances to the 503A list, we can't limit it by indication. We can't limit by uses.

There may be some uses that cause adverse events, it's possible, but we know that there are uses for which this bulk drug substance is needed for certain other uses. So we may limit it to the types of routes of administration, but we recommend something go on a list for what it's being evaluated for, and we don't limit it for other particular uses because we don't have the ability to do so. We have to rely on the provider

who's writing a patient-specific prescription for the patient, to write the prescription for the use and to appropriately monitor the patient.

DR. GULUR: Thank you, Dr. Bormel.

Dr. Bui?

DR. BUI: Yes. Dr. Bui here.

A question for Dr. Wolfert; first my comments. I commend the agency for the commitment to make the safety information available to the public. That's very helpful to the public. My question is relating to pediatric patients. You mentioned dosing.

What's the lowest age group that oxitriptan can be used for pediatric patients?

DR. WOLFERT: The evaluation for these patients begins with, let's say, an abnormal newborn screen at birth. Once the BH4 deficiency is identified and a concern for neurotransmitter depletion or derangement has been identified, my understanding is it would be started as early as possible. There is recommended dosing in the literature in the newborn age group. That might be a starting dosage of 1 to 2 mgs per kg per day, which would be slowly titrated up, but it is indicated

in that age group once diagnosed.

DR. BUI: Thank you. No --

DR. WOLFERT: I can certainly offer that question to our colleagues in the Division of Medical Genetics Emergencies, if they have anything else to add.

MS. SMPOKOU: Yes. Hi. Can you hear me?

DR. GULUR: Yes.

DR. SMPOKOU: Yes. I don't have anything else to add. I completely agree with the answer. This is Dr. Smpokou from our rare diseases team. Thanks.

DR. BUI: Thank you. No more questions for me.

DR. GULUR: Thank you.

Do we have any other questions for our presenters?

(No response.)

DR. GULUR: Seeing as there are none, we will be opening the open public hearing session.

I would like to state into the record that there are no open public hearing speakers for this topic. The open public hearing portion of this meeting has now concluded and we will no longer take comments from the audience.

Are there any further clarifying questions for the presenters? Or we will consider this the start of the panel discussion, and we are open to comments from panel members as well.

(No response.)

Dr. Vaida? Yes. Just one other question, then. Is there any data from 2019 until current that it's been used under the new guidance?

DR. BORMEL: This is Gail Bormel. I believe the data we have is really the calls that we received and the documents that we received, letting us know that this was important to be used in compounding for this particular use and that it needed to continue. That's all the data that we have that the guidance was necessary, and it has been well received, but it's anecdotal.

DR. VAIDA: Okay. Thank you. No further questions.

DR. BORMEL: Just so you know, Dr. Vaida, we don't receive information on what pharmacies are making, what state-licensed pharmacies, what federal facilities, and what licensed physicians are compounding under

Section 503A. There's no way for that information to be reported to us. Currently, we just don't receive that.

DR. VAIDA: Okay. Thank you.

DR. GULUR: Thank you.

Are there any other comments or discussion points?

(No response.)

Committee Discussion and Vote

DR. GULUR: Seeing as there are none, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee, as well as the public comments.

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

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

DR. STEVENSON: Question 4 is a voting question. Voting members will use the Adobe Connect

platform to submit their vote for this meeting. After the chairperson has read the voting question into the record and all questions and discussion regarding the wording of the vote question are complete, the chairperson will announce that the 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 as there are no questions, I will now read the question into the record.

FDA is proposing that oxitriptan for oral administration be included on the 503A Bulks List. Should oxitriptan for oral administration be placed on the list?

Any questions or concerns with the wording of this question?

(No response.)

DR. GULUR: I do not see any raised hands.

I will clarify that 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 a 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 the voting on the question for oxitriptan.

(No response.)

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 11 yeses, zero noes, 1 abstention.

DR. GULUR: Thank you.

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

We will start with Dr. McElhiney.

DR. McELHINEY: Linda McElhiney. I vote yes.

DR. GULUR: Dr. Desai?

DR. DESAI: Seemal Desai. I experienced technical difficulty during the voting and was not able to vote as a panel member. Therefore, I had to abstain.

DR. GULUR: Sorry to hear that, Dr. Desai.

Dr. Fensky?

DR. FENSKY: Tim Fensky. I voted yes.

DR. GULUR: Padma Gulur. I voted yes.

Dr. Rebello?

DR. REBELLO: Elizabeth Rebello. I voted yes.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Robin Bogner. I voted yes, and I'd like to say I stand corrected. We do revisit the bulks list when things are not accepted the first time. Thank you.

DR. GULUR: Thank you, Dr. Bogner.

Dr. Gura?

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

DR. GULUR: Dr. Sun?

DR. SUN: Jeanne Sun. I voted yes.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Yes. Allen Vaida, and I voted yes. My only comment is I wish we could have stayed with the current guidance. Thank you.

DR. GULUR: Thank you, Dr. Vaida.

Dr. Patel?

DR. PATEL: Hi. Kuldip Patel. I voted yes.

DR. GULUR: Dr. Gupta?

(No response.)

DR. GULUR: Dr. Gupta, are you muted?

(No response.)

DR. GULUR: Dr. Gupta, are you able to record your vote?

DR. GUPTA: I voted yes. Hello?

DR. GULUR: Yes. We can hear you now.

DR. GUPTA: Yes. I voted yes. Thank you.

DR. GULUR: Thank you.

Ms. Fusco-Walker?

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

DR. GULUR: Thank you.

With that, I believe we recorded everyone's vote.

Dr. Stevenson, could you confirm?

DR. STEVENSON: Yes, I can confirm. Thank you.

DR. GULUR: Thank you.

DR. STEVENSON: With this, we have ended the oxitriptan topic. We will take a five-minute break before we reconvene at 5:20 Eastern time for neomycin sulfate. Panel members, please remember that there should be no chatting or discussion of the meeting topics with other panel members during the break. Thank you.

(Whereupon, at 5:10 p.m., a recess was taken.)

DR. GULUR: We will now have Dr. Takyiah Stevenson read the Conflict of Interest Statement for this meetings Withdrawn or Removed list.

Conflict of Interest Statement

DR. STEVENSON: The Food and Drug Administration is convening today's meeting of the

Pharmacy Compounding Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the National Association of Boards of Pharmacy, NABP; the United States Pharmacopeia, USP; and the industry representatives, all members and temporary voting members of the committee are special government employees or regular federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of this committee's compliance with 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.

During the session, the committee will discuss the revisions FDA is considering to the Withdrawn or Removed List. FDA is now considering whether to amend

the rule to add one more entry to the list, neomycin sulfate, all parenteral drug products containing neomycin sulfate, except for of ophthalmic or otic use, or when combined with polymyxin B sulfate for irrigation of the intact bladder.

As previously explained in the Federal Register of July 2, 2014, 79FR 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 product on the list.

This is a particular matters meeting during which specific matters related to neomycin sulfate will be discussed. Based on the agenda for this meeting

and all financial interests 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 waiver are described in the waiver document, which are posted on FDA's website at https://www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees.

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

To ensure transparency, we encourage all standing committee members and temporary voting

members to disclose any public statements that they have made concerning the 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. Jeanne Sun is a representative member from the United States Pharmacopeia, USP.

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

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

With respect to FDA's invited industry

representative, we would like to disclose that Drs. Michael Bui and Gus Bassani 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 Kadmon Pharmaceuticals and Dr. Bassani is employed by Professional Compounding Centers of America, PCCA.

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 other participants to advise the committee of any financial relationships that they may have with the topic at issue.

Thank you very much, and I will turn it back to the chairperson, Dr. Gulur. Thank you.

DR. GULUR: Thank you, Dr. Stevenson.

We will now proceed with the FDA presentation on the Withdrawn or Removed List process from Gabriel Cosel.

FDA Presentation – Gabrielle Cosel

MS. COSEL: Good afternoon. I will provide brief remarks on FDA's process for identifying drugs for 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 Federal Food, Drug, and Cosmetic Act is that the compounder does not compound a drug product that appears on the list published by the Secretary of drug products that have been withdrawn or removed from the market because such product, or their components, have been found to be unsafe or not effective. This is known as the Withdrawn or Removed List. A drug product that is included in the Withdrawn or Removed List is not eligible for the exception exemption provided in Section 503A or 503B.

FDA periodically reviews available information on drugs withdrawn or removed from the market because such drugs or their components have been found to be

unsafe or not effective with the goal of identifying possible new entries for this list.

The information we review may include Federal Register notices announcing withdrawal of approval of a new drug application or an 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. In these cases, appropriate divisions within the 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 the information that documents its recommendations as to whether to include the drug on the Withdrawn or Removed List, or remove the drug from the list, or modify an entry.

FDA will update the Withdrawn or Removed List

through notice and rulemaking as stated in the final rule published in October of 2016. While we intend to propose regulations to revise the list when we identify drugs that we tentatively determine should be listed, we also intend to propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing.

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

As was mentioned today, we are discussing the following entries for potential inclusion on the list, and that is neomycin sulfate; all parenteral drug products containing neomycin sulfate, except for ophthalmic or otic use, or when combined with polymyxin B sulfate for irrigation of the intact bladder. That concludes my slide. Thank you.

DR. GULUR: Thank you.

We will now proceed with the FDA presentation

on neomycin from Dr. Jae Ho Hong.

FDA Presentation – Jae Ho Hong

DR. HONG: Hi. Good afternoon. My presentation is regarding the review of neomycin sulfate for the listing in the Withdrawn or Removed List. First, I'll go over the review of Withdrawn or Removed List, then I'll present the background of neomycin sulfate, including description, regulatory history, adverse reactions with parenteral use, and labeled indications, then we'll address our assessments and recommendations.

As a reminder, under Section 503A and 503B of the FD&C Act, FDA has established a list of drug products that were withdrawn or removed from the market because these drugs have been found to be unsafe or not effective.

Neomycin sulfate is an aminoglycoside antibacterial drug that was discovered in 1949. It is active against Pseudomonas, Klebsiella, Proteus, E. coli, and Enterobacter. It is poorly absorbed in the GI tract. The currently approved formulations of neomycin sulfate include oral tablets and solution,

ophthalmic, otic, and dermatologic products, and a solution for bladder irrigation, which is in combination with polymyxin B.

Following is the regulatory history of neomycin. Initially, neomycin was approved for intramuscular injection for serious systemic infections and urinary tract infections; intraperitoneal instillation for the treatment and prevention of peritonitis; intestinal instillation in abdominal surgery; and topical use.

In 1972, labeling guidelines for neomycin sulfate sterile powder was amended, stating that the intramuscular neomycin sulfate may be indicated in the treatment of urinary tract infections, and due to its toxicity, limited the use to when other alternatives are not available. Also, the label included a boxed warning regarding nephrotoxicity, ototoxicity, and respiratory paralysis due to neuromuscular blockade.

The Anti-Infective Advisory Committee meeting in 1977 concluded that there is no use of neomycin sulfate in sterile vials for parenteral use for the labeled indication and that the risk-benefit for

parenteral neomycin sulfate did not warrant its continued marketing. For the non-sterile neomycin sulfate bulk for prescription compounding, the committee concluded that a warning label should be placed.

In 1979, FDA proposed to revoke provisions for certification of neomycin sulfate in sterile vials for parenteral use based on the findings of the Anti-Infective Advisory Committee, and to revoke provisions for certification of non-sterile neomycin sulfate for prescription compounding; then in 1988, FDA revoked the provisions for certification of neomycin sulfate in sterile vials for parenteral use.

FDA amended the provisions for certification of non-sterile neomycin sulfate for prescription compounding by changing the product name to neomycin sulfate for compounding oral products and required labeling of appropriate uses and warnings about the risks with inappropriate use.

FDA withdrew approval of four applications for neomycin sulfate in sterile vials for injection in 1988 and also proposed to withdraw six applications for non-sterile neomycin sulfate products for prescription

compounding, and subsequently withdrew five of these applications. The remaining last application was withdrawn in 2019, as the holder of this application waived its opportunity for a hearing.

The systemic exposure to neomycin sulfate by parenteral administration, including intravenous or intramuscular administration, instillation or irrigation of body cavity structures or spaces, or from use in wet dressings, may cause the following adverse reactions: nephrotoxicity, irreversible ototoxicity, neuromuscular blockade, and respiratory paralysis.

The following is the currently approved oral and irrigational neomycin sulfate products and their indications. First, neomycin oral tablet is indicated for adjunctive therapy in hepatic coma and as a part of the regimen for suppression of the normal bacterial flora of the bowel.

Neomycin oral solution is indicated as an adjunctive therapy in hepatic coma. Neomycin sulfate in combination with polymixin B solution is indicated for urinary bladder irrigation of abacteriuric patients to help prevent bacteriuria and gram-negative septicemia

associated with the use of indwelling catheters.

The assessment of the approved formulations of neomycin sulfate, including formulations for oral administration, ophthalmic, otic, or dermatologic use, and in combination with polymyxin B sulfate for irrigation of the intact bladder, remains favorable. However, all other parenteral neomycin sulfate formulations may result in significant systemic exposure to neomycin and be associated with serious adverse reactions such as nephrotoxicity, ototoxicity, and neuromuscular blockade leading to respiratory paralysis.

Therefore, we recommend the following statement to be added to the Withdrawn or Removed List. All parenteral drug products containing neomycin sulfate, except when used for ophthalmic, or otic use, or in combination with polymyxin B sulfate for irrigation of the intact bladder, to be added to the Withdrawn or Removed List. This is the end of my presentation. Thank you.

DR. GULUR: Thank you.

We will now take clarifying questions for FDA presenters. Please use the raised-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 question with, "That is all for my questions," so we can move on to the next panel member.

With that, do we have any questions?

(No response.)

Open Public Hearing

DR. GULUR: Seeing none, we will now begin the open public hearing session.

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

presentation.

For this reason FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the product and, if known, its direct competitors. For example, this financial information may include the payment by a bulk drug supplier or compounding pharmacy of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you at the beginning of your statement to advise the committee if you do not have any such financial relationship. If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

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

goals today is for this open public hearing to be conducted in a fair and open away, 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 are representing for the record.

DR. CAROME: Hello. Can you hear me?

DR. GULUR: Yes, we can, Dr. Carome.

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

Regarding neomycin, Public Citizen strongly supports the FDA's proposal to add all parenteral drug products containing the aminoglycoside antibiotic, neomycin sulfate, with the exceptions noted by the FDA, 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 exemption provided by Section 503A or Section 503B of the Food, Drug, and Cosmetic Act, the Withdrawn or Removed List.

Such action should have been taken by the agency many years ago. In 1979, more than four decades ago, the FDA first proposed taking regulatory action to remove parenteral neomycin products from the market based on widespread evidence that the drug's risks outweigh its benefits.

At that time, the fact that systemic exposure to neomycin caused serious nephrotoxicity, ototoxicity, and neuromuscular paralysis with respiratory arrest was well established, and no safe parenteral dosage regimen of the drug had been recognized. Moreover, neomycin was known to be more toxic than other FDA-approved parenteral aminoglycosides.

In 1988, more than three decades ago, the FDA issued a final rule, amending the antibiotic drug regulations to revoke the provisions for certification of neomycin in sterile vials for parenteral use, and another notice withdrawing the approval of four abbreviated antibiotic drug applications for neomycin

for parenteral use because the risks involved in the parenteral use of neomycin were judged to outweigh any benefits that might be derived from its continued availability.

In 1998, more than two decades ago, the FDA appropriately proposed including all parenteral drug products containing neomycin sulfate in its proposed rule to establish the initial Withdrawn or Removed List. However, in the final rule establishing that list that was issued in 1999, the FDA excluded parenteral neomycin products from the list because the agency had failed to take appropriate administrative actions to, one, address pending requests submitted in 1988 for hearings regarding the withdrawal of approval of applications for neomycin in sterile vials for injection and the withdrawal of approval of the applications for neomycin sulfate for prescription compounding; and, two, respond to four petitions submitted in 1988 to stay these and other agency actions related to neomycin products.

Disturbingly, the straightforward administrative actions for resolving these requests for hearings and petitions for stays of action related to

neomycin products were not completed until February 2019, more than 30 years after these requests and petitions had been submitted to the agency.

The FDA's decades-long delay in placing all parenteral drug products containing neomycin, with the previously noted exceptions, on the Withdrawn or Removed List is unacceptable and borders on regulatory malpractice. The agency now must move swiftly to place parenteral drug products containing neomycin on the Withdrawn or Removed List given their unacceptable risk-benefit profile.

The following comments relate to FDA's process for updating the Withdrawn or Removed List.

While the case of neomycin is an extreme example of unacceptable delays in adding dangerous drugs to the Withdrawn or Removed List, there are many examples over the past decade of drugs not being added to this list until at least several years after the FDA had determined that the drugs had been withdrawn or removed from the market because they had been found to be unsafe or not effective.

Delaying such regulatory actions poses

unacceptable and avoidable risks to patients and public health. Therefore, in April 2021, Public Citizen petitioned the FDA to take the following actions.

1) Promptly amend, through notice and comment rulemaking, the Withdrawn or Removed List to include all drugs containing potassium hydrochloride and all drugs containing the antibiotic bacitracin; and

2) Promptly implement a policy stipulating that whenever the FDA issues a notice announcing a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness, the agency simultaneously will issue an NPRM proposing to amend the Withdrawn or Removed List.

Regarding lorcaserin, on March 4th of this year, the FDA announced in the Federal Register that the agency had determined that lorcaserin tablets, marketed under the brand names Belviq and Belviq XR for weight loss, were withdrawn from sale for reasons of safety or effectiveness, and that the agency would not accept or approve ANDAs for lorcaserin tablets. The FDA noted in its notice that results of a required postmarket trial to evaluate the risk of cardiovascular problems

suggested an imbalance in cancer in humans.

The FDA further stated the following:

"Although chance effects cannot be ruled out, the imbalance in cancer persisted throughout multiple analysis approaches. The clinical findings corroborated by the evidence from animal models informed the agency's assessment that the risks outweigh any potential benefits for the current indications. These findings were considered clinically meaningful and could not be adequately addressed through labeling. Additional evidence would be necessary to investigate this 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 and clinical studies would first need to be conducted. To address these concerns, the agency has determined that this product would not be considered safe and effective if it were reintroduced into the market."

Regarding parenteral drug products containing bacitracin, on March 12th of this year, the FDA

announced in the Federal Register that the agency was withdrawing approval of five ANDAs for bacitracin for injection from multiple holders. The FDA noted the following in its notice.

"Bacitracin for injection is an antibiotic for intramuscular administration, the use of which is limited to the treatment of infants with ammonia and empyema caused by staphylococci shown to be susceptible to the drug. Bacitracin for injection poses serious risks, including nephrotoxicity and anaphylactic reactions. Healthcare professionals generally no longer use bacitracin for injection to treat infants with pneumonia and empyema because other effective FDA-approved treatments are available that do not have these risks.

"In April 2019, an FDA advisory committee met and discussed the safety and effectiveness of bacitracin for injection. The advisory committee voted almost unanimously that the benefits of bacitracin for intramuscular injection do not outweigh its risks, including nephrotoxicity and anaphylactic reactions for the drug's only approved indication."

The FDA notice reasonably can be read as a determination by the agency that bacitracin for injection was withdrawn from sale for reasons of safety or effectiveness.

Moving forward, the FDA should not delay initiating the rulemaking process for amending the Withdrawn or Removed List once the agency has published a determination that a drug product was withdrawn from sale for reasons of safety or effectiveness. Instead, whenever the FDA announces such a determination, it simultaneously should issue an NPRM, proposing to amend the list to include that drug product. Such simultaneous action could shorten the rulemaking process for amending the list by several months to years.

Although section 503A(c)(1) of the FDCA stipulates that the FDA must convene and consult with an advisory committee before implementing changes to the Withdrawn or Removed List, it allows the agency to issue such regulations before consultation with an advisory committee if it determines that doing so is necessary to protect public health.

Such a determination certainly could reasonably

be made in all cases in which the FDA has determined that the drug was withdrawn or removed from the market because it was unsafe, and likely could reasonably be made in most cases in which the FDA has determined that a drug was withdrawn or removed from the market because it was ineffective.

Nevertheless, if the agency feels it must seek advice from its committee before issuing a final rule amending the Withdrawn or Removed List, the agency could schedule a meeting of the advisory committee for shortly after the NPRM proposing to amend the list is published.

Such expeditious regulatory action would minimize the period during which patients could be potentially harmed by exposure to compounded formulations of drug products that were determined to have been withdrawn or removed from the market for reasons of safety or effectiveness. Delaying such regulatory action poses unacceptable and avoidable risks to patients and public health. Thank you for your attention.

DR. GULUR: Thank you, Dr. Carome.

We will now take clarifying questions for the

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

Are there any clarifying questions of our presenters?

(No response.)

Committee Discussion and Vote

DR. GULUR: Seeing none, we are now in the panel discussion phase and invite comments and discussion from our panel members.

I see Dr. Bassani. Do you have a question or a comment?

DR. BASSANI: Yes, I do have a comment. This is Gus Bassani, industry non-voting member.

Just speaking from the perspective of someone in the industry, I agree with FDA's recommendation. I'm not aware of neomycin being compounded into injectables or other parenteral dosage forms that would raise concerns.

FDA has clearly articulated that the addition to the Withdrawn or Removed List does not include ophthalmic, otic, topical, oral and bladder

instillations with polymyxin B, so the wording is appropriate. Thank you.

DR. GULUR: Thank you, Dr. Bassani.

Do we have any other comments or questions?

(No response.)

DR. GULUR: Seeing as there are none, the committee will now turn its attention to address the task at hand, the careful consideration of the data before the committee as well as the public comment. We will proceed with the questions to the committee and panel discussions. I would like to remind public observers that while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Today's question is a voting question. Dr. Takyiah 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 discussions regarding the

wording of the vote question are complete, the chairperson will announce the 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 the vote is closed.

Next, the vote results will be displayed on the screen. I will read the vote result 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. GULUR: Seeing as there are none, I will read the question into the record.

FDA is proposing that neomycin sulfate, all parenteral drug products containing the neomycin sulfate, except when used for ophthalmic or otic use, or in combination with polymyxin B sulfate for irrigation of the intact ladder, be added to the Withdrawn or Removed List under Section 503A and 503B of the FD&C Act. Do you agree?

Do panel members have any concerns with the wording of this question?

(No response.)

DR. GULUR: Seeing none, if there are no questions or comments concerning the wording of the question, we will now begin the voting on the question for neomycin sulfate.

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 12 yeses, zero noes, and zero abstentions.

DR. GULUR: Thank you.

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

We'll start with Dr. McElhiney.

DR. McELHINEY: Linda McElhiney. I vote yes.

DR. GULUR: Ms. Fusco-Walker?

MS. FUSCO-WALKER: Sandra Fusco-Walker. I vote

yes.

DR. GULUR: Dr. Fensky?

DR. FENSKY: Tim Fensky. I vote yes.

DR. GULUR: Padma Gulur. I vote yes.

Dr. Gura?

DR. GURA: Kathleen Gura. I vote yes.

DR. GULUR: Dr. Bogner?

DR. BOGNER: Robin Bogner. I vote yes.

DR. GULUR: Dr. Rebello?

DR. REBELLO: Elizabeth Rebello. I vote yes.

DR. GULUR: Dr. Sun?

DR. SUN: Jeanne Sun. I vote yes.

DR. GULUR: Dr. Patel?

DR. PATEL: Kuldip Patel. I vote yes.

DR. GULUR: Dr. Vaida?

DR. VAIDA: Allen Vaida. I vote yes.

DR. GULUR: Dr. Desai?

DR. DESAI: Seemal Desai. I vote yes, and would like to point out I voted via the backup email mechanism.

DR. GULUR: Thank you, Dr. Desai.

Dr. Gupta?

DR. GUPTA: Dr. Gupta, and I voted yes.

DR. GULUR: Thank you.

Dr. Stevenson, have we recorded all votes?

DR. STEVENSON: Yes.

DR. GULUR: Thank you.

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

(No response.)

Adjournment

DR. GULUR: Seeing none, I would like to take this opportunity to thank the FDA for holding an excellent session and to all the presenters for their diligent work and presentations. It was extremely helpful to the committee as we made our decisions.

I would also like to take this opportunity to thank all the nominator presentations, as well as the public for their comments and opinions, which are of immense value in the decision-making process. And I'll end by thanking my fellow panel members.

Thank you for your work today and for your patience as we worked through a few technical issues and the delayed start. Again, thank you for everything with

regards to your efforts here, and I'll take a special moment to thank Takyiah Stevenson for her efforts in helping make this as smooth as possible for us, as well as her team.

We will now adjourn the meeting. Thank you.

(Whereupon, at 6:09 p.m., the afternoon session was adjourned.)